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### PROLAN AND ESTRIN IN THE SERUM AND URINE OF DIABETIC AND NONDIABETIC WOMEN DURING PREGNANCY, WITH ESPECIAL REFERENCE TO LATE PREGNANCY TOXEMIA\*

O. WATKINS SMITH, PH.D., AND GEORGE VAN S. SMITH, M.D.,  
BROOKLINE, MASS.

WITH THE COOPERATION OF ELLIOTT P. JOSLIN, M.D., AND  
PRISCILLA WHITE, M.D., BOSTON, MASS.

(From the Fearing Research Laboratory, Free Hospital for Women, Brookline, Mass.,  
and The George F. Baker Clinic of the New England Deaconess  
Hospital, Boston)

ALTHOUGH careful studies have revealed certain biochemical variations from the normal in the blood and urine during pregnancy, none is as striking, from a quantitative point of view, as the hormonal changes thus far demonstrated; namely, in the amounts of the anterior pituitary-like, gonad-stimulating factor (prolan of placental origin) and estrogenic substances (estrin). Undoubtedly there are marked endocrine changes associated with other organs besides the placenta as indicated morphologically (e.g., pituitary, ovaries, adrenals, and thyroid), but the analysis of blood and urine by any methods approaching quantitative standards is still limited to prolan and estrin, and even with these the shortcomings of existing procedures render the results only approximately accurate.

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The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

The importance of the interplay between all the hormones is being realized more and more. For this reason our studies can be evaluated as covering only two of many factors in a complicated equation. Notwithstanding the limitations of the present technic of assay, we have found that the prolactin and estrin of the blood and urine follow remarkably consistent curves throughout normal pregnancies, and have also detected unmistakable variations from these curves in cases of late pregnancy toxemia, exclusive of nephritis. Whether or not any etiologic significance may be attached to these variations, can for the present be only a matter for conjecture. They do suggest possible therapeutic approaches.

Assays for these two hormones in the blood and urine of 69 pregnant women and in 26 placentas have already been reported.<sup>1-4</sup> Thirty-eight per cent of the cases were normal, 42 per cent had mild to severe preeclamptic toxemia and 20 per cent had eclampsia. The results indicated that excessive amounts of prolactin and a tendency toward low levels of estrin were characteristic of the toxemias (exclusive of nephritis) and that this abnormality was of placental origin.

One patient, from whom repeated specimens were analyzed during gestation, showed an abnormal rise in serum prolactin two months before the development of clinical toxemia. A single specimen of serum from another patient contained high prolactin; a month later toxemia appeared. We were especially interested in confirming this last finding. Since the incidence of late pregnancy toxemia is high in diabetics, the study of these cases seemed to offer the best chance of being able to ascertain whether or not toxemia might be detected before it becomes clinically manifest.

In this paper are presented curves of prolactin and estrin based on the study of 27 pregnant women, 11 with diabetes, from as early as possible in gestation to delivery. Six patients, four of them diabetics, developed preeclamptic toxemia. Seventeen, including five diabetics, went through uneventful pregnancies and were delivered of normal, living infants. The remaining four pregnancies were neither strictly normal nor yet frankly toxemic and will be considered separately.

The method used in quantitating prolactin in urine and serum has been the same as that previously described.<sup>2</sup>

In assaying serums, urines, and placentas for prolactin (A.P.L.), a double end-point phenomenon has been encountered and deserves mention. We have considered the smallest amount of material, extracted and administered by the Aschheim-Zondek technic to immature rats, nineteen to twenty-one days old, which produces grossly visible discrete corpora lutea by the ninety-sixth hour the prolactin end-point. Often, however, a second end-point appears: e.g., extracts of 2.0 c.c., 1.5 c.c., and 1.0 c.c. of a given serum give corpora lutea, while 0.7 c.c., 0.5 c.c. and 0.3 c.c. result grossly in the so-called A effect, cystic uterus, and follicle ripening; but in the rats receiving 0.2 c.c. and 0.1 c.c. corpora are again found. In other words,



the serum might be considered to contain either 100 or 1000+ R.U. per 100 c.c. Davy, comparing the weights of ovaries at various injection levels, reports a similar observation.<sup>6</sup>

The first corpus luteum end-point values have formed uniform curves throughout normal pregnancies. The second end-points have been most inconsistent, being entirely absent in some specimens and in others giving results up to 30 times those indicated by the first end-point. No relationship could be established between the second end-point findings and the time of gestation or the condition of the patient.

We are at a loss to explain adequately this phenomenon. Probably stimulation of the rats' own hypophyseal luteinizing hormone by the estrin of the follicle ripening produced by smaller amounts of A.P.L. plays a part in giving the second appearance of corpora.<sup>7</sup> The prolan A effect with the larger quantities of A.P.L. may in some way be associated with antibodies, either in the extracts themselves or in the rats, due to the injected material.<sup>8, 9</sup> It is also likely that this phenomenon is related both to the number and time of injections, and to the amount given each time. Since the second end-point appears to be involved in more complex interactions, it seems advisable to present our results in terms of the first end-point figures.

For the determination of urinary estrin we have employed acid hydrolysis of specimens prior to extraction or assay,<sup>5</sup> since this method yields such high and apparently reliable values (see Charts 3 and 7).<sup>\*</sup> The placentas of 8 of the diabetic patients have been analyzed for prolan and estrin by the same technic as that previously reported.<sup>4</sup>

#### EXPERIMENTAL RESULTS

Charts 1, 2, 3, and 4 summarize in graph form the data collected on the normal nondiabetic pregnancies. In 1927 Margaret Smith reported a constant increase in whole blood estrin from early in pregnancy to delivery.<sup>10</sup> During the first three months of normal pregnancy we have been unable to demonstrate estrin in 10 c.c. of serum. The urinary estrin (hydrolyzed urines) has never amounted to more than 5,000 R.U. in twenty-four hours. From then on, the level of estrin in both serum and urine increases, the most rapid and marked rise being apparent during the last trimester. The values for urinary estrin given by unhydrolyzed specimens are included in the chart to demonstrate the inadequacy of assaying untreated urine. Smith reported a marked increase in whole blood estrin during and shortly before labor. In two of our cases, Mrs. L. D. Y. and Mrs. D. G., the serum estrin level was found to be no higher during labor than two to four weeks earlier. Mrs. L. D. Y.'s serum actually contained less one-half hour before delivery than at the eighth month (and the estrin content of her amniotic fluid was the same as that of the serum). It may well be that the partition of estrin between cells and serum changes.

<sup>\*</sup>The high "total" estrin content of urines from women over three months pregnant makes extraction of the hydrolyzed specimens unnecessary. Five or 10 c.c. (depending upon the period of gestation and the twenty-four-hour volume) are measured into a 200 c.c. volumetric flask. Fifteen volumes per cent of concentrated HCl are added and the flask heated inside the steam bath (temp. 100° C.) for one hour. The contents are diluted to volume with water, mixed, and tested directly on the rats.

Chart 1. Serum Oestrin (r.u. per 100 cc.) Non-diabetics, normal pregnancy.

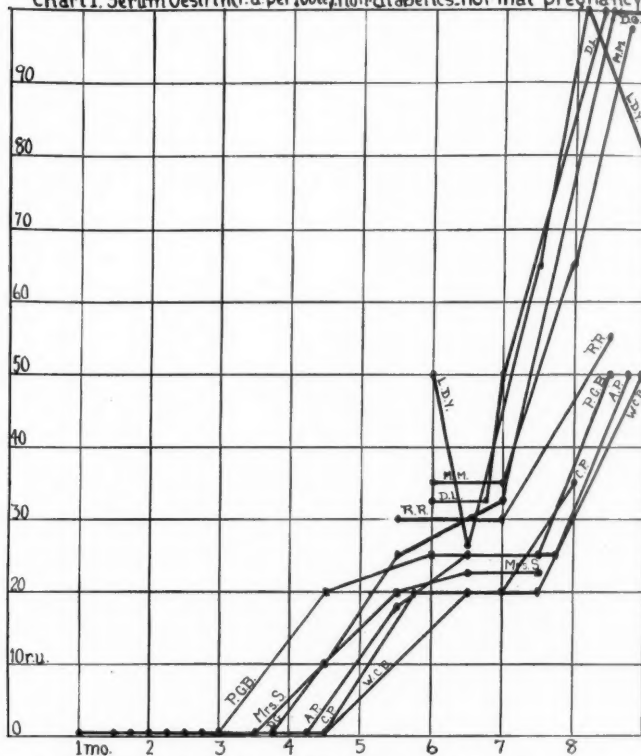
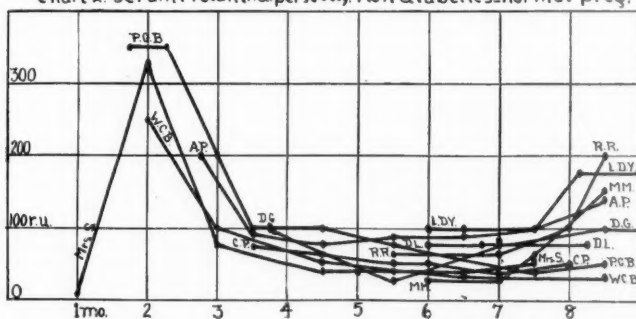


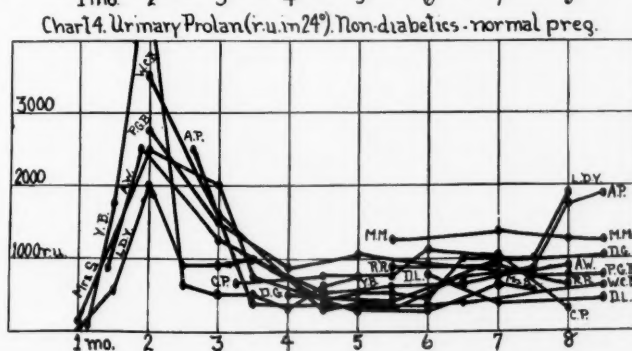
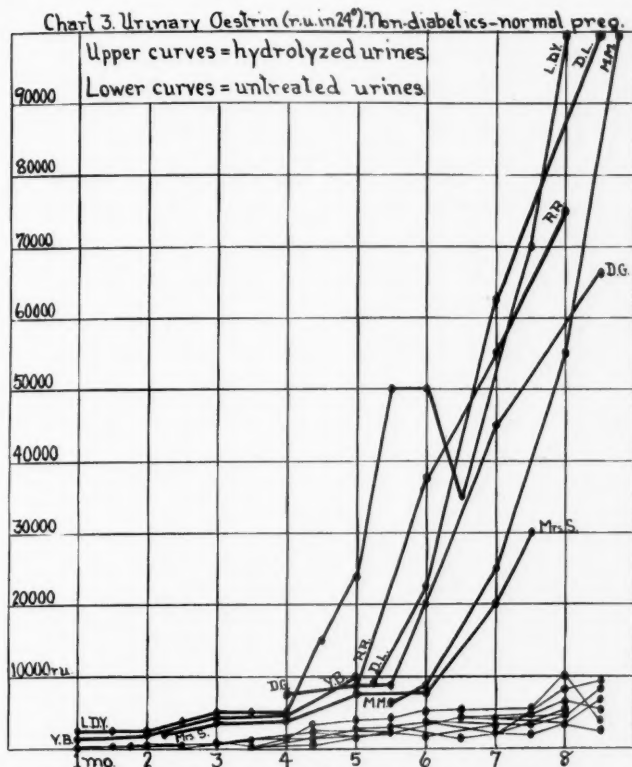
Chart 2. Serum Prolan (r.u. per 100 cc.) Non-diabetics, normal preg.



Charts 1, 2, 3, and 4.—Nondiabetics, normal pregnancies. All but two of these patients went through uneventful pregnancies and had normal deliveries at term.

Mrs. S. spontaneously ruptured her membranes and delivered a premature infant at seven and one-half months. Her prolactin and estrin curves did not differ from the normals, other than in a tendency towards low estrin levels.

Mrs. L. D. Y. began having severe uterine cramps at five and one-half months. At six months, it being apparent that both serum and urinary estrin were abnormally high, she was given 600 rat units of antophysin (Winthrop Chemical Company's A.P.L. preparation) and 21 rabbit units of prolactin (Schering Corporation's progestin) during the course of ten days. This was followed by a drop in the estrin level in both serum and urine. The clinical benefit of the treatment was doubtful, for, although the cramps were less severe following injections, they recurred intermittently from six and one-half months to delivery, which was at full term and normal. The last blood specimen on this patient, and also on Mrs. D. G., was taken during labor.



In 1928 Zondek<sup>11</sup> reported that prolan reached its highest level between the second and fourth month and from then on decreased moderately to delivery. The analyses of both serum and urine in our series of normals revealed a peak in prolan at about two months. By the beginning of the fourth month the prolan had dropped to a comparatively low level, which was maintained to the last month of pregnancy when, in several cases, a rise was apparent.

Charts 5, 6, 7, and 8 present the prolan and estrin curves on the two nondiabetic and the four diabetic women who developed preeclamptic toxemia. In four of these, in contrast with the normals, the serum estrin did not rise during the last two months. In the only three cases

Chart 5. Serum Oestrin (ruper 100u). Late pregnancy toxæmia.

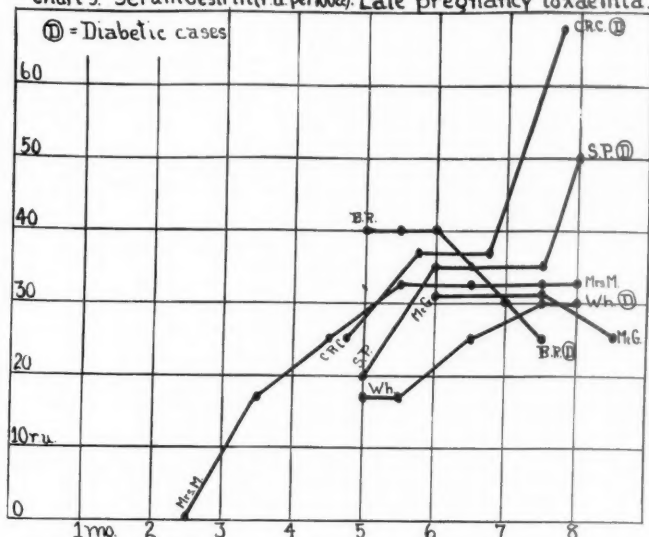
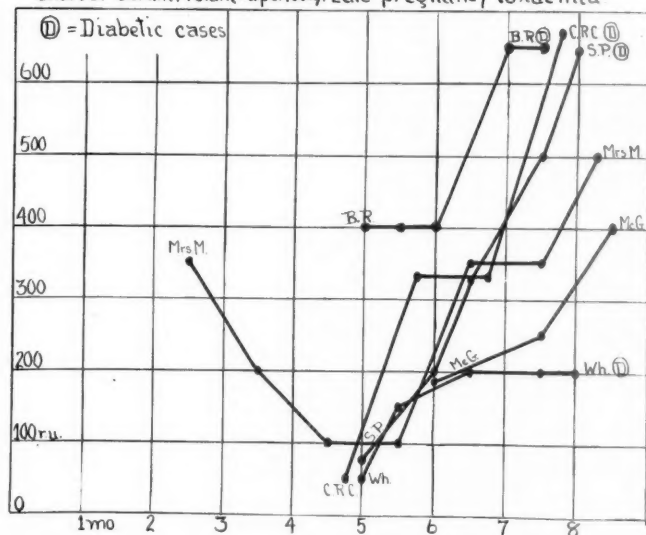


Chart 6. Serum Protan (ruper 100u). Late pregnancy toxæmia.



Charts 5, 6, 7, and 8.—Cases of late pregnancy toxæmia.

Mrs. M. (Nondiabetic.) Clinically normal to the beginning of the eighth month; then slightest possible trace of albumin in urine. At eight and one-half months blood pressure 140/90; albumin, trace; edema, +++. Induced delivery one week before term of a normal, living infant.

Mrs. McG. (Nondiabetic.) At seven and one-half months, blood pressure, 140/90; otherwise normal. At eight and one-half months, blood pressure, 150/110, albumin, slight trace; edema, +++. Normal delivery of a normal, living infant ten days before term.

Mrs. S. P. (Diabetic.) Diabetes well controlled throughout pregnancy with 35 to 50 U. insulin daily. Slight edema at seven months; otherwise normal. At eight months, blood pressure, 140/80; albumin, trace; edema, +++. Early in the eighth month a ten and three-fourths pound, edematous infant was delivered by cesarean section.

(Continued on opposite page.)

Chart 7. Urinary Oestrin (ru in 24) Late pregnancy toxæmia.

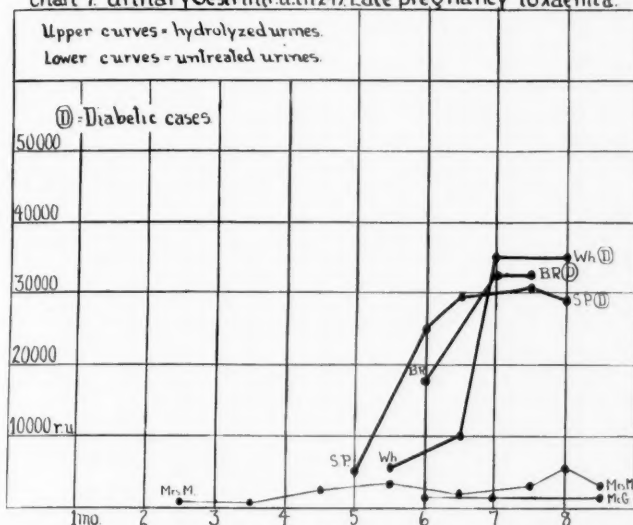
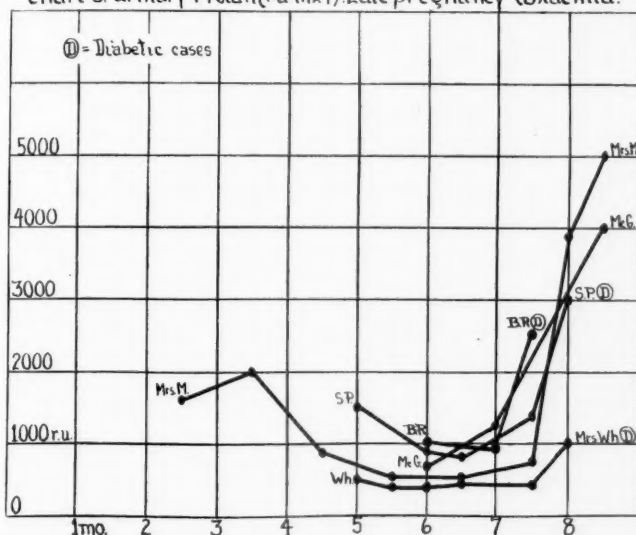


Chart 8. Urinary Prolan (ru in 24) Late pregnancy toxæmia.



Mrs. Wh. (Diabetic.) Diabetes well controlled throughout pregnancy with 50 U. insulin daily. At seven and one-half months slight edema and slightest possible trace of albumin; otherwise normal. At eight months, blood pressure, 160/110; albumin, large trace; edema, +++. The last specimen was taken one day before the death of the fetus, which event was followed by cessation of toxæmia. Delivery of a large macerated fetus occurred five weeks later.

Mrs. C. R. C. (Diabetic.) Diabetes fairly well controlled with 40 U. insulin daily. No symptoms of toxæmia until end of seventh month. Then, within a few days, blood pressure, 160/110; albumin, very slight trace; edema, +++. Delivered immediately by cesarean section of a fat but not typically edematous infant weighing 6 pounds and 13 ounces.

Mrs. B. R. (Diabetic.) Severe diabetes well controlled with 30 to 60 U. insulin daily. Slight rise in blood pressure and a trace of albumin at seven months. At seven and one-half months, blood pressure, 172/104; albumin, large trace; edema, +++. Delivered by cesarean section of a normal infant weighing five pounds and five ounces.

Chart 9. Serum Oestrin (r.u. per 100cc) Diabetics-normal pregnancy.

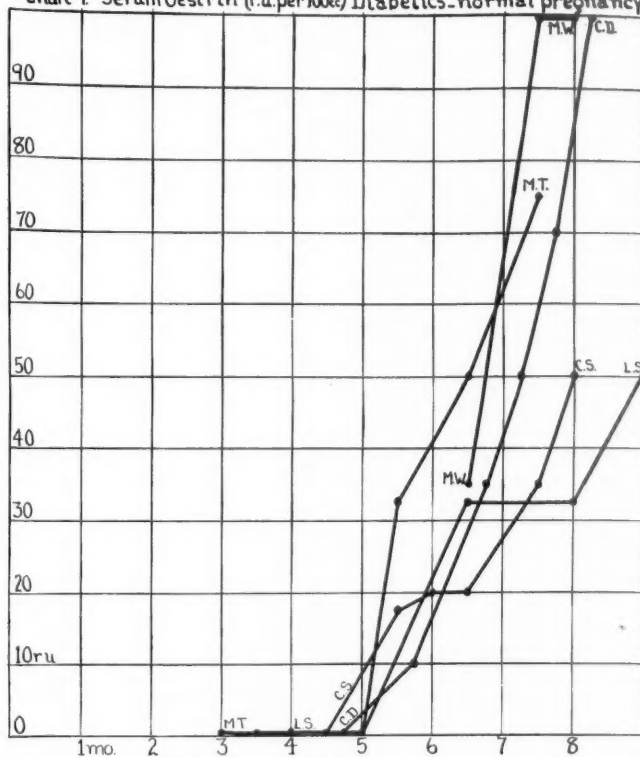
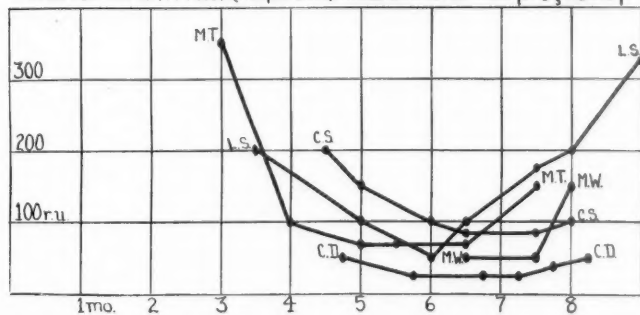


Chart 10 Serum Prolan (r.u. per 100cc) Diabetics-normal pregnancy.



Charts 9, 10, 11, and 12.—Diabetics, normal pregnancies.

Mrs. M. T. Diabetes well under control throughout pregnancy with 35 to 50 U. insulin daily. Intermittent nausea and vomiting during first five and one-half months. (Note rise in estrin coincident with cessation of nausea.)<sup>3</sup> Delivered by cesarean section early in the eighth month of a normal, 6 pound 6 ounce infant.

L. S. Very mild diabetes; no insulin required. Normal delivery at term of a 5½ pound, living infant.

Mrs. C. S. Diabetes well controlled throughout gestation with 30 to 60 U. insulin daily. Delivered by cesarean section early in the eighth month of a normal, 8 pound, living infant, which died three hours later. Autopsy diagnosis: prematurity.

Mrs. M. W. Diabetes controlled with 50 U. insulin daily. Delivered by cesarean section early in the eighth month of a normal, 5 pound, living infant.

Mrs. C. D. Diabetes impossible to control; 80 U. insulin a day. Delivered by cesarean section early in the eighth month of a normal, 6 pound 11 ounce, living infant. Hydramnios.



Chart 11. Urinary Oestrin(ru in 24). Diabetics..normal pregnancy.

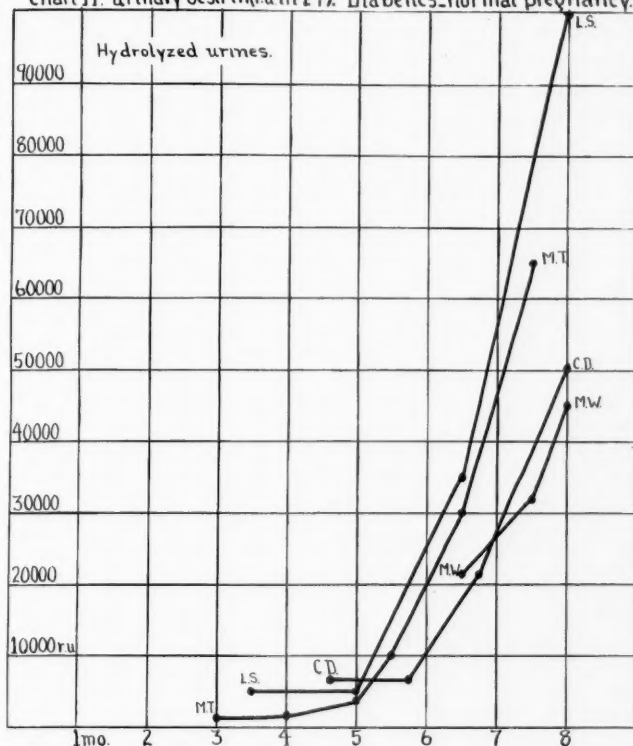
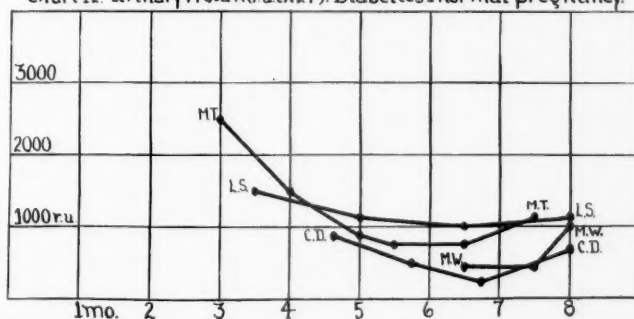


Chart 12 Urinary Prolan(ru in 24). Diabetics..normal pregnancy.



whose urines were assayed after hydrolysis, the excretion of estrin failed to increase after the seventh month. These estrin abnormalities were not demonstrable until shortly before the appearance of toxemia.

The serum prolan of all these cases began to rise during the second trimester and at no time after the beginning of the sixth month was it less than 200 R.U. per 100 c.e. These curves contrast markedly with the normal in which, without exception, the serum prolan from the fourth to the eighth month was 100 R.U. or less per 100 c.e. *The rise in serum prolan was apparent in each case of late pregnancy toxemia at least six weeks before the clinical diagnosis could be made. Prolan*

Chart 13. Serum Oestrin (r.u. per 100 cc.) Abnormal cases.

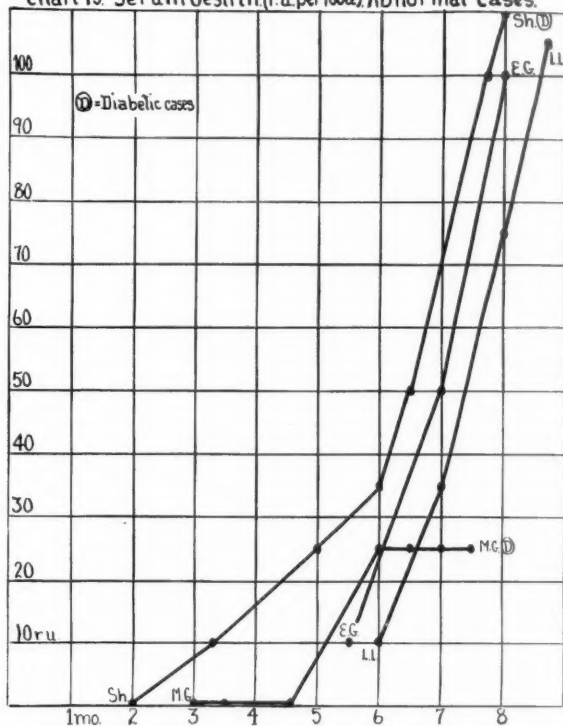
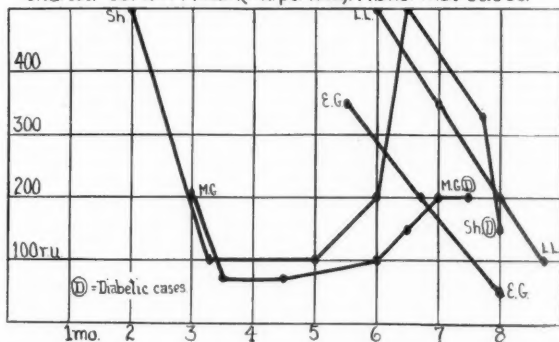


Chart 14. Serum Prolan (r.u. per 100 cc.) Abnormal cases.



Charts 13, 14, 15, and 16.—Four abnormal cases.

Mrs. M. G. (Diabetic.) Diabetes well controlled throughout gestation with 8 to 28 U. insulin daily. Hydramnios but no signs of toxemia. At seven and one-half months spontaneous premature delivery of a 7½ pound, edematous, giant infant, which lived only twenty minutes. Autopsy revealed hemorrhagic disease, rickets and scurvy.

Mrs. Sh. (Diabetic.) Diabetes controlled with 20 U. insulin per day. At eight months a large trace of albumin appeared in the urine; otherwise clinically well. Delivered early in the eighth month of an 8¾ pound, edematous, giant infant.

E. G. (Nondiabetic.) Normal gestation until the middle of the seventh month, when a trace of albumin appeared in the urine. This continued until delivery, which was full term and normal. No other signs of toxemia.

L. L. (Nondiabetic.) Normal pregnancy except for a rise in blood pressure during the last month to 158/80. Delivery was at full term and normal.

Chart 15 Urinary Oestrin (ru. in 24) Abnormal cases

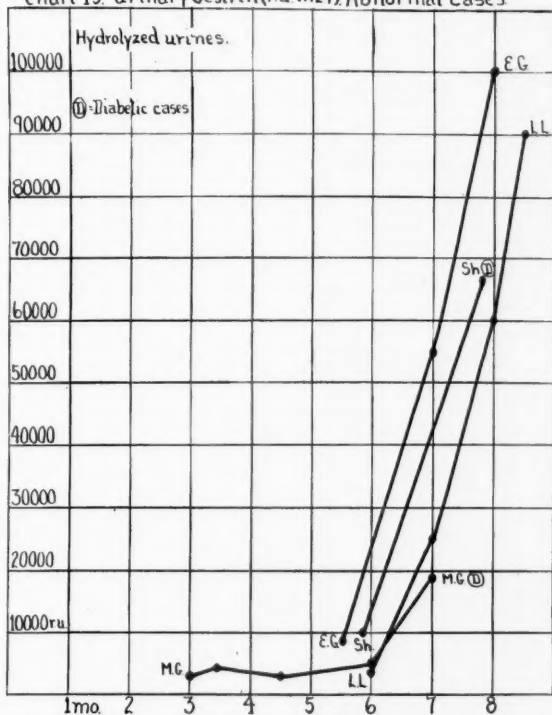
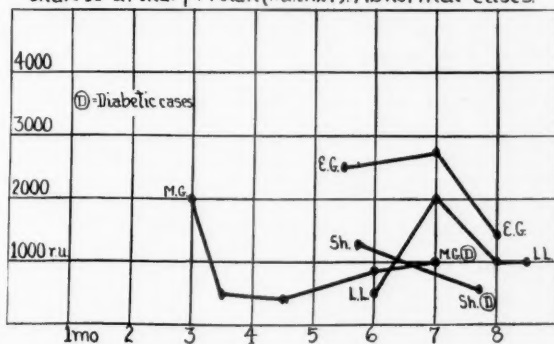


Chart 16 Urinary Prolan (ru. in 24) Abnormal cases



excretion was high in four of the five patients whose urines were assayed, but not until the clinical diagnosis had been made. This lag in prolactin excretion in the toxemias seems to us to be of especial interest and importance, since in all the other curves the prolactin and estrin levels for serum and urine run roughly parallel. There was no variation of the prolactin or estrin findings in the four toxemic diabetics that might differentiate them from the nondiabetic cases with toxemia.

Mention should be made of these patients' infants. The two nondiabetic patients had normal, living babies. Of the diabetics, Mrs. S. P. was delivered by cesarean section early in the eighth month of a ten and three-fourths pound, living,

edematous, giant infant. The second, Mrs. Wh., delivered a large macerated fetus five weeks after it had died. Mrs. C. R. C., the third, was delivered by cesarean section shortly before the eighth month because a rise in blood pressure and marked edema suddenly developed. The living infant was large but not typically edematous. Mrs. B. R. was delivered at seven and one-half months by cesarean section of a five-pound, normal, living baby.

Charts 9, 10, 11, and 12 contain the curves on five diabetic women who went through pregnancy without accident and were delivered (four by cesarean section) of normal, living infants. In general the prolactin and estrin levels follow the same curves as those for the nondiabetic normals. There is a tendency, however, toward a later drop in serum prolactin, a later appearance of demonstrable serum estrin, and an earlier and more pronounced rise in the serum prolactin toward term. In other words, the curves vary slightly from the normal nondiabetic in such a way as to suggest that they approach the toxemic borderline. This departure may be linked with the high incidence of toxemia in diabetic pregnancies.

Two diabetic patients, not included in the charts, had premature deliveries immediately after the first specimens were taken, one at six and the other at seven months. Neither had toxemia and their babies were not edematous. Their prolactin and estrin levels were within the limits of normal. Among the few nondiabetic cases of miscarriage and premature delivery that we have studied, no typical prolactin or estrin abnormalities have been evident.

Charts 13, 14, 15, and 16 present the analyses on four women who could not be grouped either as definitely toxemic or strictly normal. In all of them the appearance of excessive serum prolactin at five to seven months led us to predict late pregnancy toxemia.

Mrs. M. G., diabetic, delivered a premature, markedly edematous infant at seven and one-half months. She had a hydramnios but no clinical evidence of toxemia. Both prolactin and estrin curves were entirely comparable with those of the toxemics.

Mrs. Sh., diabetic, showed a rise in prolactin at six months and a high level at seven months, but her estrin was rising too. At eight months a large trace of urinary albumin appeared. However, between the seventh and eighth month the prolactin decreased and her estrin rose markedly. Albuminuria continued to delivery, but there was no other evidence of toxemia. Her infant was a typical diabetic giant.

E. G. and L. L., two nondiabetics, showed curves entirely similar to those of Mrs. Sh., i.e., high prolactin near the sixth month followed by a drop coincident with a marked increase in estrin. E. G. had only albuminuria; L. L. had a rise in blood pressure. Both delivered full-term, normal, living infants.

From the results demonstrated in the first twelve charts, our interpretation of these four cases would be that Mrs. M. G. might have developed toxemia had pregnancy continued; whereas in the other three the rise of estrin and drop in prolactin after the seventh month may have been associated with the fact that clinically there was only mild toxemia.

In Table I are analyses of the placentas from eight of the diabetic cases. As was found in nondiabetic pregnancies,<sup>4</sup> the placental figures confirm the blood and urinary findings and indicate also that excessive prolan is of placental origin. The analyses of Mrs. Wh.'s placenta are included to demonstrate that prolan and estrin persisted even after death of the fetus. The values, however, are presumably lower than they were when the fetus was alive and the patient toxemic.

TABLE I. PROLAN AND ESTRIN IN THE PLACENTAS FROM 8 DIABETICS

CASE	CLINICAL DATA	PROLAN R.U. PER G. (DRY WT.)		ESTRIN R.U. PER G. (DRY WT.)	
		MA- TERNAL	FETAL	MA- TERNAL	FETAL
Mrs. E. D. <sup>1</sup>	Miscarried at 6 months No toxemia Baby not edematous	2.0	3.0	6.0	10.0
Mrs. E. W. <sup>1</sup>	Miscarried at 7 months No toxemia Baby not edematous	3.0	4.5	15.0	15.0
Mrs. M. W. <sup>2</sup>	Normal pregnancy Cesarean at 8 months Baby not edematous	4.5	2.0	6.0	10.0
Mrs. M. T. <sup>2</sup>	Normal pregnancy except for early nausea Cesarean at 8 months Baby not edematous	3.0	6.0	15.0	10.0
Mrs. C. S. <sup>2</sup>	Normal pregnancy Cesarean at 8 months Baby not edematous	3.0	4.5	10.0	15.0
Mrs. S. P. <sup>3</sup>	Late pregnancy toxemia Cesarean at 8 months Baby typical diabetic giant	45.0	60.0	6.0	3.0
Mrs. M. G. <sup>4</sup>	Miscarried at 7½ months No toxemia. Hydramnios Baby typical diabetic giant	18.0	30.0	7.5	6.0
Mrs. Wh. <sup>3</sup>	Late pregnancy toxemia Baby died 5 weeks before de- livery	6.0	6.0	5.0	5.0

<sup>1</sup>Urinary and serum values not included in charts, well within the limits of normal.

<sup>2</sup>For urinary and serum values, see Charts 9, 10, 11, and 12.

<sup>3</sup>For urinary and serum values, see Charts 5, 6, 7, and 8.

<sup>4</sup>For urinary and serum values, see Charts 13, 14, 15, and 16.

#### DISCUSSION

One of the most striking features of these charts is the fact that high levels of serum prolan are almost invariably associated with low estrin and vice versa. In the normal pregnancies estrin was not demonstrable in 10 c.c. of serum until the prolan had dropped from the two-month peak. In the toxemias the abnormal rise in serum prolan was followed by a leveling-off or drop in serum estrin during the last trimester, at which time the normal curves showed their greatest estrin rise. The diabetics who went through pregnancy normally showed a somewhat later drop in serum prolan than the nondiabetic normals, together with a later appearance of demonstrable serum estrin. The mutually antagonistic action of these two hormones is particularly indicated in the three cases of very mild toxemia presented in Charts 13, 14, 15, and 16. We have previously demonstrated that the administration of prolan (A.P.L.) to pregnant women resulted in a temporary lowering of the level of estrin.<sup>12</sup> We have also, in two cases (Case 21,<sup>2</sup> and Case 1,<sup>13</sup> found

that the administration of large amounts of estrin resulted in a temporary lowering of prolan. Although our present state of knowledge does not justify the assumption of high prolan as an etiologic factor in the toxemias of late pregnancy, the results presented do point toward estrin as an experimental therapeutic measure.

In a previous communication<sup>4</sup> we advanced the hypothesis that toxemia might be the result of a diffuse and vicarious menstrual-like process occurring in pregnancy. Clinically the analogy is weak. Mild to severe edema or an increase in weight at the time of menstruation has been reported. The various disturbances at menstruation reflect an upset of the sympathetic nervous system. (In this category also could be included cases of functional flowing, especially menopausal.) The above hypothesis was suggested by our hormonal studies from which we now associate the onset of toxemia with high prolan and relatively low estrin. The consensus of opinion is that both normal menstruation and functional bleeding in women and experimental bleeding in monkeys follow a drop in estrin. In nine out of ten instances we have found a rise in urinary prolan (probably hypophyseal) before or at menstruation. Moreover, increased prolan (probably hypophyseal) has been reported in a large percentage of women with functional bleeding.<sup>14, 15</sup> The analogy is strengthened by the pathology of toxemia, which is characterized by changes due to and associated with edema, necrosis, and capillary thrombosis and hemorrhage, all of which processes point to arteriolar spasm as the common denominator,<sup>16</sup> and this in turn implicates the sympathetic nervous system. Edema, necrosis, capillary thrombosis, and hemorrhage are typical findings in the endometrium at menstruation and are in part characteristic of the endometrium of functional bleeding. It has recently been announced<sup>17</sup> that arteriolar spasm initiates the endometrial bleeding of monkeys. From these pathologic considerations the theory seems tenable that cases of toxic separation of the placenta are the result of actual menstruation during pregnancy, while toxemia might well be due to the same process taking place vicariously rather than in the endometrium alone.

This theory suggests another therapeutic approach. Menstruation has been inhibited in monkeys<sup>18</sup> by the giving of sufficient progestin. There is growing evidence that human menstruation can be prevented by progestin. The possibility of progestin therapy in late toxemia is, therefore, appealing.

We are now attempting to compare the progestin content of placentas from normal and toxemic cases, but, although the hormone can be identified in this organ, the present methods of assay are not sensitive enough to make comparative analyses significant.

#### SUMMARY

Analyses on 12 nondiabetic women throughout normal pregnancies indicate that the peak in prolan of both urine and serum occurs at approximately two months and that by the beginning of the fourth month this hormone reaches a lower and fairly constant level coincident with an increase in estrin. The most rapid rise in estrin of both urine and serum takes place during the last trimester.

The data on 6 cases of late pregnancy toxemia (4 of them diabetics) confirm the previously reported finding of high prolan and low estrin in this condition and demonstrate that *the abnormal rise in serum prolan precedes the clinical manifestations by at least six weeks.*

The curves on 5 diabetic women throughout normal pregnancies are essentially similar to those of the normal nondiabetics. A somewhat later rise in estrin and a less marked plateau of prolan suggests, how-



ever, that the high incidence of toxemia in diabetic pregnancies may be linked with a prolan-estrin imbalance which approaches the toxemic borderline.

In 4 cases, two diabetic patients, high serum prolan at five to seven months led to the prediction of late pregnancy toxemia. One of these women (diabetic) had a premature delivery at seven and one-half months. The other 3 showed a very marked rise in estrin during the last trimester coincident with a drop in prolan to within the limits of normal and the appearance of only very mild toxic symptoms.

Of the 11 diabetic patients followed, 4 had either stillbirths or edematous giant infants. All 4 of these women showed the prolan-estrin imbalance typical of toxemia at five to seven months. The diabetic patients with normal curves for prolan and estrin delivered normal, living infants. Two of the diabetic patients, on the other hand, whose prolan was excessive and who developed severe toxemia, were delivered by cesarean section at seven and one-half months of normal, living infants. Although it might be argued that in these two cases early delivery had preceded abnormal growth of the fetus, the data at hand are too limited to permit the establishment of any connection between the endocrine findings and the type of infant in diabetic pregnancies.

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#### Chamorro, Antonio: Autotransplant of the Ovary Into the Anterior Chamber of Female Rabbits' Eyes, Rev. españ. de obst. y ginec. (Madrid) 20: 401, 1935.

The author reviews the literature on the subject of ovarian transplants.

Autotransplantation of ovaries of rabbits into the anterior chamber of rabbits' eyes provides an excellent method for research as it permits perfect visualization of the transplant during its period of activity. Unilateral transplants do not function and soon disappear. Bilateral transplants, however, grow without much difficulty. After maturation, two kinds of follicles develop, one with a very short cycle and the other, a persistent follicle, becomes cystic and does not respond typically to gonadotrophic stimuli. Administration of large amounts of estrogenic hormone failed to cause rupture of the follicles except in one case where a rupture of the tissues had occurred with protrusion of the follicle. The article is beautifully illustrated with colored plates.

F. L. ADAIR AND J. SUAREZ.

## DIABETES COMPLICATING PREGNANCY\*

PRISCILLA WHITE, M.D., BOSTON, MASS.

(From the George F. Baker Clinic of the New England Deaconess Hospital)

THE unfavorable effects of diabetes complicating pregnancy are manifested by: (1) accidents to the fetus; (2) maternal toxemia and eclampsia; (3) maternal coma; (4) maternal hypoglycemia. Our own medical conception of this problem is based upon an analysis of 271 pregnancies which have occurred in 191 diabetic women consulting Dr. Joslin between 1898 and October, 1935. Approximately half of these cases occurred in the preinsulin and one-half in the insulin eras. A comparative analysis of these two periods shows surprisingly slight improvement, for stillbirths have dropped only from 29 to 25 per cent, miscarriages and abortions from 22 to 16 per cent. We are, therefore, naturally concerned with the investigation of the manner in which diabetes appears to contribute to these accidents and in that form of treatment of the disease which most successfully avoids them.

Early abortion and miscarriage we attribute directly to a lack of control of diabetes, for their incidence was some six times greater among cases characterized by elevation of the blood sugar and glycosuria than among those patients who had more adequately controlled diabetes. Although positive evidence of such important theoretical factors as deficiency diet, a lethal factor in the primary cell, endocrine imbalance early in pregnancy, acidosis and hypoglycemia were lacking in this series, they need further investigation. The characteristic pathology of uncontrolled diabetes seems to us, however, to indicate how harmful it may be. It is known that the impregnated ovum implants itself in that portion of the uterus which has the richest supply of glycogen. Failure of the normal deposition of glycogen is a characteristic lesion of uncontrolled diabetes, and this lack of glycogen should theoretically favor imperfect nidation.

Toxemia and eclampsia occur nearly fifty times more frequently in the diabetic than they do in the nondiabetic childbearing population at large. These conditions are more common in the younger and, consequently, the severer cases. The severity of diabetes rather than its control favors the development of these complications. That toxemia may be the consequence of diabetes is indicated by the newer physiologic research which seems to show that toxemia is associated with an abnormal hormonal state probably related to the placenta, that diabetes is a disease of interglandular relationships and that there are other similar

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clinical manifestations of endocrine disturbance, particularly in the youthful diabetic. Examples are the failure of growth which amounts to actual dwarfism in some diabetic children, retarded maturity, and the long periods of amenorrhea in the adolescent.

Stillbirth is a third, perhaps, related failure. For years the obstetric diabetic literature has contained accounts of the frequency with which an overdeveloped, macerated fetus has been born to the diabetic mother. Here we wish to emphasize that this is not an unfailing characteristic of diabetes. The very fact that nearly half of all these pregnancies ended successfully prior to the general use of insulin shows without further comment that this is not the case. The cause of this overdevelopment, characteristic of so many of these pregnancies, has never been quite clear. It is natural that it should be attributed to overnutrition, to the elevation of blood sugar and blood fat, to the products of acidosis, and to hypoglycemia. Signs of these were lacking in our own series. Repeatedly it has been our experience, as well as that of others, that with a perfectly controlled case the fetus has died two, four, or six weeks prior to term. Yet the opposite situation with acidosis and even coma has occurred in this same apparently critical period, and patients have later been delivered of normal living children. Although it is granted that all of these factors need further investigation, still a new and interesting clew appears in the demonstration of an excess of serum prolactin (Smith and Smith). That prolactin is a substance capable of producing gigantism has been demonstrated by Snyder<sup>1</sup> and Hoopes,<sup>2</sup> who have independently shown that injections of prolactin produce exactly the picture we see in diabetes, overdevelopment, death, and maceration of giant rat and rabbit fetuses. Thus, we believe that two definite forward steps have been made: first, when Dr. Titus decided to deliver these patients prematurely to anticipate the death of the fetus in utero, a procedure which was not entirely satisfactory, for we knew that not all of these patients were predestined to the development of this complication; second, when as appears now to be the case, we have a biologic test which indicates the cases in which the fetus is of the giant type described as characteristic of diabetes.

Congenital defects, hypoglycemia and asphyxia complicate the neonatal period. Congenital defects are doubtless beyond our therapeutic control. They are, we believe, related to a disease which is genetic in origin. It is an interesting association here to note that Priesel and Wagner<sup>3</sup> have already reported the great frequency with which congenital anomalies occur in the true juvenile diabetic patient.

Hypoglycemia may be a dangerous complication in the neonatal period. It may result from a maternal overdose of insulin, or it may be due to an overproduction of fetal islet tissue. Hyperplasia of the fetal islands of Langerhans has been reported seven times<sup>4</sup> in the literature, twice it has been known to occur with an elevation of blood sugar,

once with a perfectly normal blood sugar, and three times with a slightly subnormal blood sugar. Among our last 17 cases coming to term, we have been making various blood chemical analyses, and once we observed a blood sugar which was slightly subnormal, 60 mg. This infant subsequently developed the whole train of symptoms which we associate with an insulin reaction in a juvenile patient, namely a sudden onset of sweating, pallor followed by cyanosis, twitchings, and convulsions. The blood sugar was found to have fallen to 9 mg. or one-tenth of the normal value. The symptoms were quickly relieved by the administration of glucose given by gavage. At the time we thought this was an example of spontaneous hypoglycemia, the first we had ever seen, but now we are afraid it was due to an overdose of insulin, for although the mother's blood sugar was perfectly normal, 70 mg., when she was on the operating table, her blood sugar too fell to subnormal levels and she had symptoms of hypoglycemia. Furthermore, the baby's blood sugar became stabilized on the third day. We doubt that this would have occurred with overproduction of endogenous insulin.

Asphyxia may be a serious problem in the neonatal period. It may result from the long labor which will occur in many of these pregnancies because of the large size of so many of the babies. Then too insulin itself is capable of producing cerebral edema, but, perhaps most important of all, because the acid base balance of a child of a diabetic mother is disturbed. Eastman<sup>5</sup> has found that the carbon dioxide content of the blood of children born after relatively short labor was 48 volumes per cent, but this figure dropped to 40 volumes per cent with more difficult labor and anesthesia and to 38 volumes per cent in children who had severe asphyxia. In the infants of our series the average carbon dioxide combining power was 35 volumes per cent, the range being from 19 to 52. Earlier in this discussion we said that we did not think that the interoccurrence of acidosis during the early part of the third trimester was so harmful to the fetus. During labor it may be harmful, because if the alkali reserve of the mother's blood drops to less than 10 volumes per cent, a finding not unusual in diabetic coma, there will be associated with it a low oxygen content. This may have a serious effect upon the fetus, occurring when it is about to establish an independent existence. Even without acidosis asphyxia is a real problem and these babies particularly require plenty of oxygen, with proper aspiration, perhaps alpha lobeline or even a Drinker respirator.

Congenital diabetes<sup>6</sup> is a rare occurrence. There are some eight, presumably authentic, cases reported in the literature, but the data are not very striking. Among the 170 infants represented in this series, one, a fatal case, had an elevation of blood sugar above normal; one subsequently developed diabetes at the age of four years.

The temporary unfavorable effects of pregnancy upon the course of diabetes are largely four: change in tolerance for carbohydrate; lower-

ing of the renal threshold; predisposition to coma; and predisposition to hypoglycemia. The change in tolerance for carbohydrate, measured either by the insulin requirements or the elevation of blood sugar, on the average in this series was negligible. Individual cases, however, showed a wide variation, the greatest change generally occurring in the third trimester, when some patients who had required 50 units of insulin prior to pregnancy gave it up entirely until after delivery, and others required twice their former dose.

A low renal threshold generally occurred in the second trimester. The cause of this condition is not clear. It resembles the benign type of glycosuria associated with disturbances of the glands of internal secretion and is, perhaps, the result of changes in the endocrine glands, coincident with pregnancy.

Pregnancy favors the interoccurrence of acidosis because of the normally lowered alkali reserve, the depletion of glycogen, and the increased basal metabolic rate. The last two factors favor the interoccurrence of the opposite complication, hypoglycemia.

Thus the treatment of the diabetic during pregnancy will vary with problems of the individual patient and with the problems of each trimester. In the first trimester we will be concerned not only with the dietetic control of nausea and vomiting, the readjustment of the diabetic regime which this complication necessitates, but also with the accurate control of diabetes, which we believe prevents spontaneous abortion. If hourly feedings of carbohydrate food or parenteral glucose must be given, then we abandon our usual routine for insulin and administer it according to what Dr. Joslin likes to term "the emergency prescription," testing the urine every two, four, or six hours, giving 20 units of insulin if the Benedict test is red, 15 if orange, 10 if yellow, and 5 if yellow green. If nausea and vomiting do not complicate the first trimester, then there will be little need of readjusting the diabetic regime.

In the second trimester we are concerned with a low renal threshold and with the increased requirement for food. Here, to prevent hypoglycemia in the presence of glycosuria, we believe it is better to base changes in the dosage of insulin upon blood sugar analyses rather than upon urinalyses.

In the third trimester we are concerned over the possible development of acidosis. By this time the basal metabolism has become elevated to 20 per cent above normal, and the mother will require a definite increase in the number of calories. It has been estimated that the fetus metabolizes 50 gm. of glucose daily, and an allowance for this must be made in the mother's diet, so that we plan to give a minimum of 150 gm. of carbohydrate, 1 gm. of protein per kilogram of actual body weight, and 30 calories per kilogram of actual body weight.

Labor increases the complications of the third trimester, increases depletion of glycogen, and increases basal metabolic rate. If the patient



is to be delivered by normal labor, then she will require first of all constant attendance because she is a potential coma case. The carbohydrate intake should vary from 150 to 300 gm. with large quantities of fluid. If the patient is delivered by cesarean section, there is danger of the interoccurrence of hypoglycemia, and since our experience with the infant whose blood sugar fell to 9 mg., we have been much happier when we have maintained a maternal blood sugar between 150 and 200 mg. than at that level which might be considered more ideally normal. After cesarean section the management of diabetes is that of any surgical case, specimens being tested every three hours and insulin prescribed according to the degree of reduction in the Benedict test.

Thus the diabetic during pregnancy is a candidate for coma in the first trimester, hypoglycemia in the second, acidosis, toxemia, and hypoglycemia in the third, and if she has normal labor, then the danger of coma is great and, perhaps, very serious indeed.

Another failure of many diabetic pregnancies is that of lactation. This has been observed in the diabetic animal as well as the diabetic woman.<sup>7</sup> It is, perhaps, due to the lack of the specific lactogenic hormone of the pituitary gland. We think it is not related to calories, because it has occurred when the mother's diet contained between 2,500 and 3,500 calories and when we believe it to be adequate in all respects. Puerperal sepsis, contrary to our expectations, is rare in diabetes.

Genetic and eugenic problems arise. We believe that until the treatment of diabetes, even as good as it is today, improves, the diabetic should not have numerous pregnancies. Diabetes is a chronic, potentially incapacitating disease, predisposing the patient, even in youth, to a premature development of old age manifested by arteriosclerosis, retinal hemorrhages, cataracts, and diabetic neuritis. One must remember in treating these patients that the actual age is not the chronologic age, but as Dr. Joslin has pointed out, far more nearly the chronologic age plus the duration of diabetes.

Perhaps most important of all, we must answer the question, what are this child's chances of inheriting diabetes? We believe that we have presented evidence that the potentiality for developing diabetes is inherited insidiously through a simple Mendelian recessive gene,<sup>8</sup> according to which theory it is necessary for both parents to contribute the genes for diabetes. A diabetic may arise from the union of two diabetics, a diabetic and an hereditary carrier, or two hereditary carriers. In calculating backward from the incidence of diabetes in the general population, we estimate that the incidence of carriers is very high, nearly 25 per cent of our entire population, so that in random mating the chances of a child of a diabetic eventually developing the disease are 1 in 4, and we must also remember that all of these children of diabetics are in turn hereditary carriers of diabetes.



In conclusion, we believe (1) that the incidence of spontaneous abortion may be reduced by more accurate control of diabetes; (2) that toxemia and eclampsia occur with great frequency, particularly in the youthful type of diabetes; (3) that related to these complications is the common complication of the diabetic pregnancy, a giant fetus; (4) that deaths in the neonatal period are largely due to congenital defects which are beyond our therapeutic control, to hypoglycemia which can be corrected, and to asphyxia to which the infant of the diabetic patient is undoubtedly more liable than that of the non-diabetic, because of the greater danger of toxemic and diabetic acidosis; (5) that the treatment of the diabetic patient during pregnancy must be individualized; (6) that the diabetic woman should not have numerous pregnancies, because diabetes carries with it a morbidity hazard, but most important of all, that the potentiality of developing the disease is inherited.

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The abnormal proliferation of the endometrium as a result of a persistent ripe follicle without ovulation has been named "glandular cystic hyperplasia." This condition is attended with ~~hyper~~erobiotic areas occurring in the thick mucosa and subsequent irregular and protracted bleeding. It is a disturbance in the genital cycle, marked by the absence of ovulation corpus luteum phase and a true menstrual process.

Wherever it was possible to examine the ovaries he confirmed the presence of ripe follicles and the absence of a corpus luteum. The cystic atretic follicles do not exert this influence on the endometrium.

The condition occurs most commonly at about the age of 40 years. Diagnosis is established by means of curettage. Pelvic examination for the determination of the size and condition of the ovaries is an essential factor.

Treatment is causal and general. Hormone therapy is indicated in the hypoplastic conditions and in menorrhagia without palpable lesions.

In atypical bleeding from a myomatous uterus myomectomy often is indicated or total hysterectomy may be required. X-ray sterilization was resorted to in a few instances. In chronic metritis radium is the treatment of choice.

F. L. ADAIR AND S. A. PEARL.

## DIABETES IN PREGNANCY FROM THE OBSTETRIC POINT OF VIEW\*

R. S. TITUS, M.D., BOSTON, MASS.

**I**NSULIN has made medical history. Insulin is making obstetric history. Before 1920 diabetes and pregnancy made a discouraging association. The only encouraging part of this association was its actual infrequency. It is well worth while to consider the reasons for this infrequency.

Before insulin the diabetic patients who developed the disease in the first and second decades of life had almost no chance of reaching maturity and motherhood, for the earlier in life the disease developed the more serious it was. In consequence, pregnancies in diabetics at that time occurred practically always in those cases in whom diabetes did not appear until the patient was in her twenties or thirties, and such cases of diabetes were recognized as being of the less severe type. When one considers that the average active fertile life of any woman is between the years of twenty and forty, and that before insulin practically none of the cases developing in the first decades survived to that age, one begins to see why the problem of diabetes and pregnancy before the discovery of insulin was numerically negligible.

Diabetes used to be considered a definite cause of sterility. Miscarriages among diabetics were recognized as probable sequelae of pregnancy. Furthermore, pregnancies occurring in these diabetics were prone to result in dead babies before viability or overdeveloped, macerated babies after eight months; it was very unusual for a case to be delivered of a living child, and it was only in the milder diabetics that pregnancy was considered a worth-while venture. Because of the reasons just enumerated, diabetics who did become pregnant were very often advised to be aborted.

The foregoing shows why pregnancy complicating diabetes was not a real problem before insulin was discovered.

What insulin has done for the general diabetic insulin is now doing for the pregnant diabetic. It has increased the fertility in those in whom diabetes occurs between the years of twenty and forty and holds the disease in check. It has saved the lives of children developing diabetes before or during the teens so that they have lived to maturity and maternity.

With the very appreciable increase in the number of diabetics who may become pregnant for the above reasons, the problem of the

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obstetric management of these cases must be given very serious thought and consideration. It is a real problem and one that more and more is going to demand definite unity of obstetric opinion. The whole problem is so young that no one really knows anything about it. There have not been enough cases upon which to base obstetric laws as to their management, so that all we say here are our own views, and have gradually evolved as case after case has taught a new lesson. We can assert from our experience that insulin makes pregnancy safe for the mother, but it does not insure fetal life to viability or survival after delivery.

As in other conditions complicating pregnancy, when no one rule as to their handling can intelligently be laid down, no one method of treatment can hope to encompass the proper treatment for all diabetics. As it is extremely unintelligent to say that all nephritics should be delivered in one fashion or that all cardiacs should be delivered in one fashion, so it is also unintelligent to say that all diabetics should likewise be delivered and handled in one fashion. Each diabetic must be individualized. The mild one certainly does not need the extreme care during pregnancy nor at term that the severe diabetic should receive. It is not intelligent to infer that the mild diabetic who has one or two children living, whose diabetes is absolutely under control, should be delivered in any but the natural manner. It is intelligent to assume that the severe diabetic, one who developed the disease as a child, who is living and pregnant because of insulin, is a very different problem and one that deserves much more thought and attention. As I have said, insulin saves the lives of these diabetics who become pregnant. It has not yet saved all the babies.

Diabetics of a severe type are advised against any added load. If they have infected teeth, these are removed. If they have a skin infection, this is watched very carefully. If they develop pneumonia, their diabetes may at once become almost uncontrollable. Is it not logical to infer that the drain of pregnancy on diabetics of this type of severity may not make subsequent pregnancies inadvisable, thus increasing the value of each pregnancy, and if this is so, is not each baby of much greater value than the individual baby in any normal pregnancy? The obstetric problem really is a reduction of the mortality of these babies. All study, all effort, all methods of delivery should attempt to provide a living child for each individual diabetic pregnancy.

We do not really know what the effect of pregnancy in after-years is on these serious diabetic mothers. Enough time has not yet elapsed for any definite conclusions upon this subject. At the present time we feel that in this type of case each individual baby, because it may seem wise that this mother should have no more babies, has a right to demand that it be delivered by that method which will guarantee, as far as is humanly and obstetrically possible, its safe arrival, without

carrying with it, of course, unnecessary morbidity to the mother; and the mother has the same right to demand a living child, if diabetes does not kill the child before viability.

Before going any further in the discussion of diabetes and pregnancy, I want to make it perfectly clear that up to the point of deciding when and how to deliver pregnant patients, the problem is a medical problem. No one should entertain the handling of these serious diabetics who is not thoroughly conversant with diabetes. The proper handling of these cases from start to finish means intelligent cooperation between the diabetic specialist and the obstetrician, and any obstetrician who is courageous enough or ignorant enough to assume the responsibility of handling these cases during pregnancy and delivery, either normal or operative, without having in attendance during the entire labor the physician expertly trained in the care of diabetes, is assuming a burden which he has no right to assume, and a burden which if assumed may well lead to the death of his patient.

All that I have to say about this subject of diabetes and pregnancy and its obstetric management is based upon what I have learned and deduced from our study of forty-three cases. Far be it from me to say that my conclusions are the only right conclusions; that my suggestions on the handling of these cases are the only right suggestions.

I shall concisely review certain of these cases, showing the successes, the failures, the pitfalls, and hoping to point out my reasons for the conclusions which have seemed intelligent and conservative rather than unnecessarily radical. No one really knows anything about this problem. With more experience the present point of view may not be at all tenable, and I realize most of all that all the babies of these diabetic mothers at the present state of our knowledge and the present handling of these patients cannot be guaranteed life.

In this series of 43 cases, one occurred before 1920. In the last two years there have been 16.

There were: 21 primiparas, 22 multiparas, 12 normal deliveries with living children, 14 cesarean sections, 5 cases of breech, 10 miscarriages or interruptions of pregnancy in the first three months, 6 hysterotomies, 2 deliveries at seven months, 4 inductions by rupturing the membranes when induction was practicable at eight and one-half months plus, 1 case of twins, 3 macerated babies, and 5 "insulin mothers" (patients who before insulin would not be alive).

There were the following complications: 2 cases of hydramnios, 3 cases of coma developing during pregnancy, 7 toxemias, 1 case of pyelitis during pregnancy, and 1 gallbladder attack during pregnancy.

Not a mother was lost.

So we see in this series that from the standpoint of the mothers, mortality and morbidity are well controlled by insulin.

In this series there were nine babies who did not survive, in pregnancies that lasted seven months or more.

From this we see that the fetal death rate, from all causes, is still tremendously high. Let us analyze these fetal deaths, and see which ones might have been prevented.

First, the patient at seven months with hydramnios, whose baby died a few hours after birth of atelectasis and hemorrhagic disease. We do not know the cause of acute hydramnios. Some day this may be prevented. We can hardly be blamed for the death of a baby at seven months of atelectasis and hemorrhagic disease. Each problem cannot begin until the infant has reached a normal viable state, and the nearer eight months or, better still, the farther beyond eight months interference is considered advisable, the better the chance on the baby.

Second, the death of a twin at eight months, who lived twenty-four hours and died of cerebral hemorrhage. This was the second of the twins, the bigger of the two. It was a simple double footling extraction, and it is very difficult to understand how the delivery caused the cerebral hemorrhage.

Third, the macerated baby at term who weighed 6 pounds, 7 ounces, and died in utero at seven months plus is another of the unavoidable disasters that pregnant diabetics must face. This patient, although a toxemic, had not advanced sufficiently to hope for the infant's surviving if the pregnancy were terminated, and the toxemia itself was not clinically severe enough to warrant interruption. These possibilities always exist. They are the unavoidable chances that diabetics must take, and the possibilities must always be told these patients when they embark on the stormy sea of a diabetic pregnancy.

Fourth, a baby dying at seven months of prematurity, the mother in labor, and ill with pneumonia. This was a breech, which lived just a few hours and weighed five pounds, twelve ounces.

Fifth and sixth, two cases of intrauterine death after viability which resulted in macerated babies. These two babies, had they been delivered after viability, might have been saved.

Finally, of the cesarean babies that did not survive, there were three, one that was delivered at eight and one-half months, who died of congenital heart, revealed at autopsy; one delivered at seven and one-fourth months, with patient in acidotic condition, beginning coma, starting labor with a living child, who weighed 7 pounds, 6 ounces, and died in ten hours of prematurity (her previous pregnancy had resulted in a dead baby at seven months); one delivered at eight months plus, who weighed 8 pounds, 1 ounce, the autopsy showing "prematurity."

Fetal deaths that occur after eight months from coma or from the fickleness of diabetes are fetal deaths that may be obviated by delivery while the child is alive. This is really the obstetric problem of the management of these cases, and if 6+ per cent of the babies in this particular series of possible living children are lost from maceration when they might well have been saved by delivery after viability, the problem is still one worthy of further consideration and study. The method of delivering these patients may well be questioned. My feeling is that in the "insulin mother," who ought to have no more than one or possibly two pregnancies, the child takes on so much added value that cesarean section is not a radical performance.



In this analysis, there are certain cases that I call key cases, that I would like somewhat specifically to point out.

CASE 1.—R. This is the only diabetic whom I took care of before the discovery of insulin, with a living child. This case is referred to merely to bring out the time element.

CASE 2.—Mrs. G., thirty-nine years old, who had had 13 pregnancies, with no living children, entered the hospital in coma at approximately six months. This is the first case in Dr. Joslin's experience in which the baby survived intrauterine life in spite of diabetic coma in the mother. Patient was delivered at eight and one-half months by cesarean section, under spinal anesthesia. This case stimulated Dr. Joslin's interest in the subject of pregnancy in diabetes, because it showed him that insulin could prevent an intrauterine death from diabetic coma, and all that has been done on diabetic patients since then has been done entirely because of Dr. Joslin's enthusiasm.

CASE 3.—Mrs. H., thirty-five years old, had had 2 previous babies, the first still-born at term, the second stillborn at seven months. This child died at approximately eight and one-half months. The delivery was normal. The baby was macerated. This was an obstetric failure in spite of insulin, a failure that delivery after eight months assuredly would have prevented.

CASE 4.—Mrs. G., twenty-one years old, had had diabetes since she was eight years old. Patient went into severe coma at the onset of labor, at which time the baby was alive. After a labor of twelve hours the baby was born with beginning maceration. The coma was deep and the patient was given a tremendous number of units of insulin. This case illustrates how tragic it is to have a baby alive now and dead in ten minutes in an insulin mother whose number of pregnancies, in the present stage of our knowledge, must be limited.

CASE 5.—Mrs. C., a primipara, nineteen years old, started in labor, with a breech, and was delivered by cesarean section. The operation was done because she was a diabetic who developed diabetes as a child, and it was done to avoid any possible fetal injury. The interesting thing about this particular patient is that she had a child that weighed seven pounds, five ounces, when, to the best of calculations, she was well under eight months.

CASE 6.—Mrs. P., a primipara, twenty-nine years old. When about six months pregnant she gained much too much weight, developed a great deal of edema and was in the hospital with a blood pressure of 130 plus and some albumin. Her uterus was big with a large amount of fluid and a good-sized baby. Because of the size of the baby and the toxemia she was delivered while under eight months, by cesarean section, of a baby weighing ten and one-half pounds, and the baby is alive and well today. This case, as well as the previous case, illustrates the size to which some of these diabetic babies develop, also the problem of toxemia that is seen not at all infrequently associated with diabetes in pregnancy.

My experience with the fourth case was so tragic, I felt so badly about having lost a baby which died under our observation that the general rule was laid down to deliver all these insulin mothers and sick diabetics by cesarean section as soon as it was felt that the baby was viable. Our experience with Cases 5 and 6 accentuated in our minds the tendency toward overdevelopment of these babies in certain diabetics, and made us wonder whether or not certain of these cases did



not superincubate their babies and develop them prematurely so that they became overripe children before nature took the initiative and started labor, with the frequent result of macerated stillbirths. Consequently, since that time cesarean sections have been done on this particular type of diabetic. All the babies are living and well with the exception of two, one that weighed 7 pounds, 6 ounces, whose autopsy showed prematurity and atelectasis, and one that weighed 8 pounds, 1 ounce, whose autopsy showed only "prematurity."

If one contemplates the delivery of these babies before labor starts, one sometimes is in a quandary as to the exact duration of pregnancy because of the absence of specific catamenial history. A few of these cases were extremely irregular, being unwell only once in six or eight weeks. One of our patients had the peculiar habit of being very irregular in the summer, and as the cold weather approached her periods appeared at a normal interval. If one feels that delivery is warranted to avoid intrauterine death and maceration after viability, one surely does not want to deliver these babies too soon. One wants to be as sure as one can be that the child is viable, that the child is big enough to survive. In the case of the overdeveloped infant, this is not a very difficult problem, but all of these diabetic babies are not overdeveloped. Some of them are small. The use of the x-ray at intervals after the patient has reached what we think is seven months may ultimately prove to be a very helpful procedure. Our experience to date with x-raying these babies to determine their size has not been particularly satisfactory, but that is no reason why the x-ray should not be used, because I am sure that its establishment as a piece of routine will ultimately be of inestimable value.

Now, just a word about the use of spinal anesthesia in these cases. The first patient upon whom we did a cesarean section was Mrs. G., and spinal anesthesia was chosen because it had been the anesthesia used in a good many of Dr. Joslin's abdominal cases. It was so satisfactory from every point of view that it has since been the routine anesthetic. The relaxation was perfect. There was no intestinal straining. There were no unpleasant sequelae following its use. The operation, because of the perfect relaxation and the absence of intestinal straining, has been done with the greatest amount of ease and celerity; and it seems that any anesthetic which makes the operation simpler, consequently consuming much less time, and avoiding the need of walling off straining intestines, is an anesthetic which has a great deal to be said for itself. I have been so impressed with its use that I have used it thirty-six times in normal cases of cesarean section and hysterotomies.

The operation of sterilization in all but one case has been done in the very simple manner described by Bishop. It is an operation which I think deserves more widespread acceptance. It takes almost no time,

it involves no possible complications and, so far as I know, no one of the patients upon whom I have performed it has since become pregnant.

No review of this subject is complete without saying something about these babies after birth. It is not nearly enough to deliver them alive. If one feels that the case may be considered successfully treated when the child is delivered living, one does not understand the problem of these newborns. Is it not fair to wonder if there is not something that we at present know nothing about inherent in these diabetic children that causes the death of one weighing 8 pounds, 1 ounce, and another weighing 7 pounds, 6 ounces, at birth? We do not expect to lose from just prematurity a child that weighs 8 pounds, 1 ounce, and another that weighs 7 pounds, 6 ounces, whose autopsies show no gross pathology. The strange reactions of some of these babies for forty-eight hours after delivery have led us to know that it takes these little infants quite some time to adjust themselves to independent living. It seems as though their metabolic reactions were all wrong, possibly because of the immediate withdrawal of the influence of the insulin that their mothers have been taking. One of our babies had convulsions, and its blood sugar was the lowest that Dr. White has ever seen. Another of our babies developed general anasarca, pitting edema appeared twenty-four hours after birth, and there was edema of the lungs. There was no blood sugar done on this child at the time, so we do not know what its blood sugar was, but twenty-four hours later it had overcome whatever was wrong and thereafter appeared and behaved like a normal infant. All of these babies must be under very expert care from the moment of delivery. Our babies are under the care of special nurses for at least forty-eight hours. Once the readjustment has satisfactorily taken place between the entirely dependent life before birth and the comparatively independent life after birth these babies have done well; but inasmuch as one of the aims of diabetes and pregnancy should be to insure living children to each diabetic mother, the care of these infants as soon as they are born must be as expertly handled as the care of the diabetic mothers up to labor and delivery.

Now, in conclusion, let me emphasize: That insulin is increasing every day the number of possible pregnancies in diabetics. That these diabetics who become pregnant must be under the most efficient medical care. That no obstetrician should think for one minute of handling these cases alone. That insulin makes pregnancy safe for the mothers. That present knowledge cannot guarantee living children. That the method of delivery must be individualized. That the baby is so very important in the severe diabetics and in the "insulin mothers" that, to avoid intrauterine death, the safest method is cesarean section when the baby seems quite big enough.

## THE ENDOMETRIAL THEORY OF ECTOPIC PREGNANCY\*

JESSE M. FRANKEL, M.D., AND SAMUEL B. SCHENCK, M.D., F.A.C.S.,  
BROOKLYN, N. Y.

*(From the Department of Gynecology of the Jewish Hospital)*

**I**N A PREVIOUS communication to this JOURNAL,<sup>1</sup> we referred to the project which forms the substance of this paper.

Six years ago while doing research work on tubal pregnancy it occurred to one of us (J. M. F.) that rarely could he satisfy himself that sufficient gynecologic pathology existed to justify the selection of an etiologic factor. It was found by him that patches of decidual tissue frequently occurred at the site of implantation of the gestation in the tube. In some specimens the decidual tissue was present only in shreds, in others in considerable amount. Out of this grew the idea that this was incidental and not accidental. In 1933, 29 patients with tubal pregnancy were operated upon at the Jewish Hospital of Brooklyn. In all of these patients the affected tube was removed. A routine section was taken by the pathologist from each specimen for histologic examination. In the pathologist's report the presence of the decidual tissue was sometimes noted, but more often not, since the search was mainly for the important diagnostic element, the chorionic villi, and the single section studied was one taken at random. Frankel went over these casual histologic slides more carefully and found that in 18 cases or 62 per cent he was able to find more or less well-defined decidual tissue. This frequency made the suspicion stronger that there might be a possible physiologic relationship between the decidual tissue and the ectopic gestation.

In 1934 we set out to find whether any such relationship existed and as a result of our research, we believe we can now set forth the following as hypotheses:

1. The etiologic factor in the production of extrauterine pregnancy is the prior existence of endometrial tissue in an ectopic site.
2. The fertilized ovum by positive chemotactic attraction migrates to the ectopic endometrial tissue and imbeds there.
3. The ultimate fate of the pregnancy depends on (a) the amount of ectopic endometrial tissue present, and (b) the depth of penetration of the ovum into the structure in which the ectopic endometrium is harbored.
4. Ectopic pregnancy is always primary and never becomes secondary; when it is extruded from the fallopian tube following rupture of that viscus or abortion through the fimbrial end, it does not continue its development.

\*Read before the Section on Gynecology and Obstetrics of the New York Academy of Medicine, December 17, 1935.

## PRESENT ETIOLOGIC THEORIES

The causes given by various authorities are very many and varied. For brevity and clarity they can all be accommodated in the following classification:

I. Causes that operate by delaying the passage of the ovum so that the active agent of nidation, the plasmodial trophoblast, is developed before the zygote reaches the uterine cavity.

A. Intratubal partial obstruction: concurrent salpingitis, postinflammatory agglutination of tubal folds, and intratubal tumors.

B. Extratubal partial obstruction: Compression, torsion or distortion of tube by tumors, peritubal inflammation, or adhesions.

C. Lengthening or kinking of the tube.

D. External migration of ovum, the wandering of the fertilized ovum to the tubal ostium of the opposite side.

II. Entrapping of the zygote in false passages so that it is forced to imbed at the place where its progress to the uterus is halted.

A. Tubal anomalies: Diverticula, accessory tubes, accessory ostia.

B. Labyrinthine branches from the true tubal lumen resulting from adhesions of tubal folds after the subsiding of gonorrheal salpingitis.

## CONSIDERATION OF THESE THEORIES

In 7 of the 29 cases above mentioned, there was definite evidence of previous inflammation of the tube. In the remaining 22 cases, none of the enumerated etiologic factors could be demonstrated at all. It was this that led to our undertaking a definite search for a common cause.

The occurrence of gestation in an anomalous tube is very rare and can be dismissed from consideration as an important cause.

External migration of the ovum is only hypothetical except in those cases where the tube on the side of the follicular rupture is absent or completely occluded, and therefore can be only an unimportant factor.

Intratubal and extratubal tumors and adhesions as potent factors were not demonstrable in any of our cases. The same can be said of kinking or stretching of the tube.

This leaves for active consideration false passages in the tubal lumen created by agglutinated tubal folds. Hahn<sup>2</sup> stated that gonorrhea is the commonest cause of extrauterine pregnancy, since this type of pregnancy is commoner in large towns where gonorrhea is more frequent and where both these conditions are increasing in frequency. Falk,<sup>3,4</sup> noted the same for this country and stated that ectopic gestation was more frequent in Harlem where the incidence of gonorrhea is notoriously higher than in certain Quaker settlements in Pennsylvania where both social diseases and ectopic pregnancies are rare. Yet it could account for only seven of our cases or 23 per cent, leaving 77 per cent unaccounted for. It was plain that our etiologic factor could not be found in those enumerated. In addition, none of these causes could account for primary abdominal pregnancy.

## PRESENTATION OF CASES

In 1934, we began to examine carefully all tubes removed at operation for whatever cause. Histologic study was made of sections through the isthmus, the ampulla, and the infundibulum of each tube. Tubes the seat of ectopic gestation were sectioned serially from end to end. To date we have examined a total of 204 cases. In 94 cases both tubes were removed at the operation, while in 110 cases only one tube was excised. This latter group includes 16 tubal gestations.

In Case 95, we found conclusively in one tube an endometrial patch in the muscular portion of the tubal wall. Cases 109 and 142, the

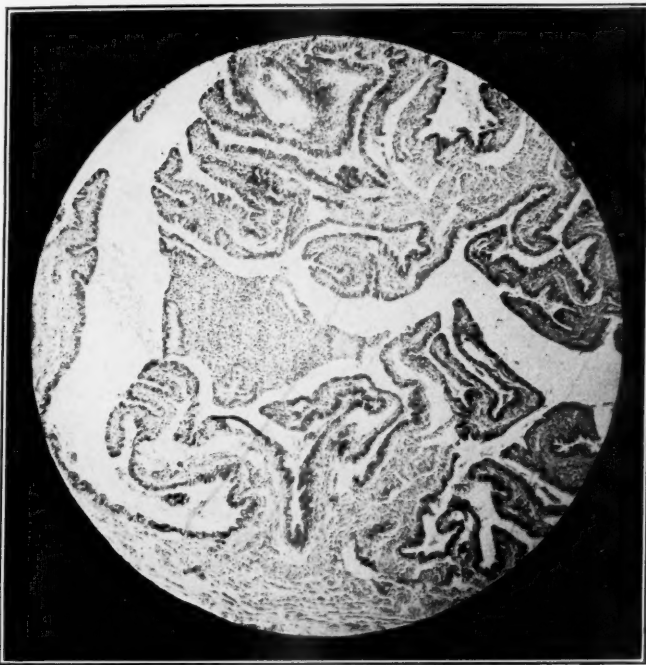


Fig. 1.—Case 109. Endometrial tissue lying in lumen of tube.

former consisting of only one tube while the latter had two tubes, only one of which contained peculiar structures, we found shreds of endometrial tissue lying free in the lumina of the tubes. In Case 158 there was a tubal gestation that contained in its decidual tissue demonstrable endometrial glands. In the 16 pregnant tubes well-defined decidual tissue was present at the implantation site, in 14 cases, and there only, while two cases were so distended by old clotted blood that, aside from the surrounding muscular wall and the contained blood clot containing a few ghosts of villi, no other structures could be made out.

The case reports are given in detail.

CASE 1 (109).—One tube removed with the uterus for fibromyomas uteri. The tubes were grossly and microscopically normal except that lying free in the lumen



was a piece of tissue consisting of tubular glands surrounded by a cytogenic stroma. That was found in the isthmic portion and ampulla portion of the tube. The infundibular section of the tube differs only in that the tissue in the lumen was in three small shreds, one of which was partly covered by columnar epithelium. These structures were readily identified with endometrium.

CASE 2 (142).—Both tubes removed with a fibromyomatous uterus. Both tubes grossly and microscopically normal. In the lumen of one tube at the ampulla was found a shred of endometrial tissue wider than in the previous case lying free.

CASE 3 (95).—Both tubes were removed with a fibromyomatous uterus and were grossly normal. One tube was microscopically normal, but the other had imbedded in the muscular wall of the tube in its ampullar part groups of tubal glands each surrounded by cytogenic stroma, each group more or less separated from the others



Fig. 2.—Case 142. Endometrial tissue lying in lumen of uterine end of tube.

by muscle tissue. This was also definite endometrial tissue and was in the nonsecretory phase. It was absent from infundibular and isthmic sections of the tube. As the ampullar joined the infundibular, the endometrial tissue was more abundant and lay close to the serous surface of the tube, while toward the isthmus the endometrium became scant and lay more deeply in the muscle.

CASE 4 (158).—Tube was removed for ectopic pregnancy. It was markedly enlarged, being 3 cm. in diameter. The surface was smooth and bluish pink. On section it was found to be distended with a blood clot in the center of which was a small smooth lined cavity. Microscopically one wall of the tube contained the blood clot in which were chorionic villi. The tubal lumen narrowed and compressed against the opposite wall, the folds being rendered more shallow and flattened. Decidual tissue was found at the periphery of the blood clot. In that portion of the decidual tissue lying on the muscle toward the periphery of the tube were found several endometrial glands. The decidual cells were individually recognizable only in spots,



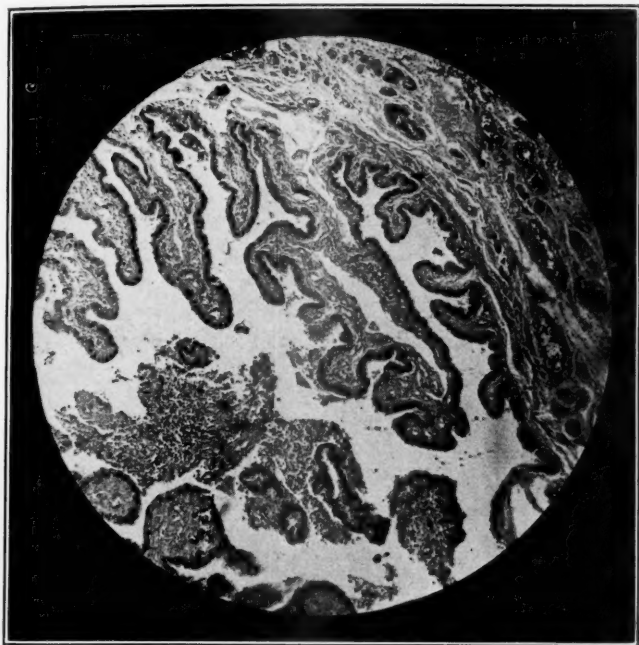


Fig. 3.—Case 142. Endometrial tissue lying in lumen of isthmus portion of tube.

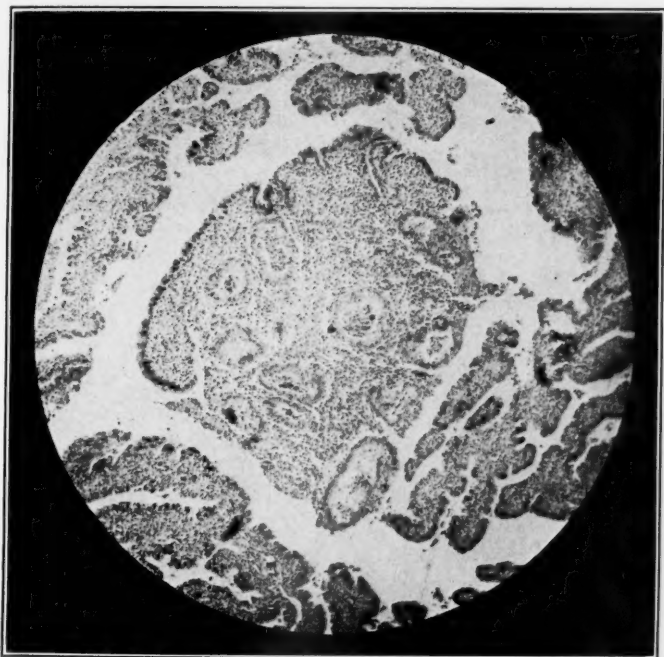


Fig. 4.—Case 142. Endometrial tissue lying in lumen of ampulla end of tube.

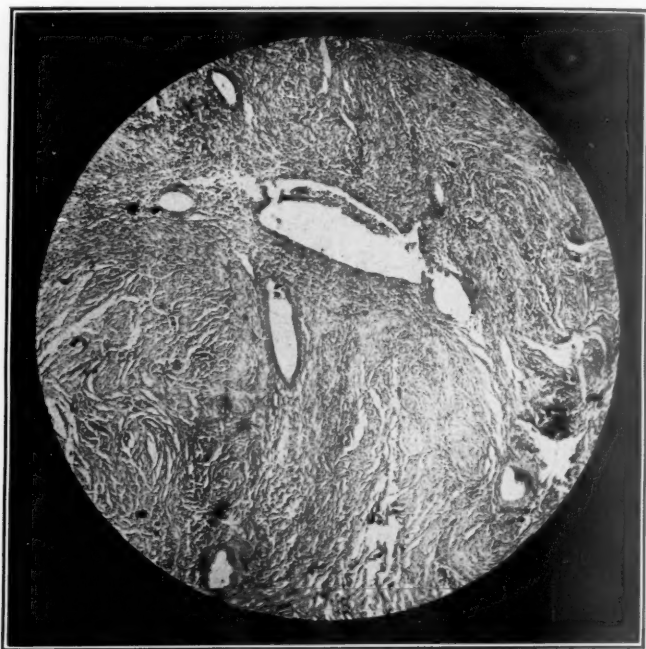


Fig. 5.—Case 95. Endometrial implant in wall of tube, abdominal end.



Fig. 6.—Case 95. Endometrial implant in wall of tube-isthmus part, glands are numerous, lie close to serous surface.

the greater portion of them being converted into the hyaline-like band of Nita-busch's fibrin layer. Other sections through this specimen showed the breaking through of the fetal elements into the tubal wall where the decidual layer was deficient.

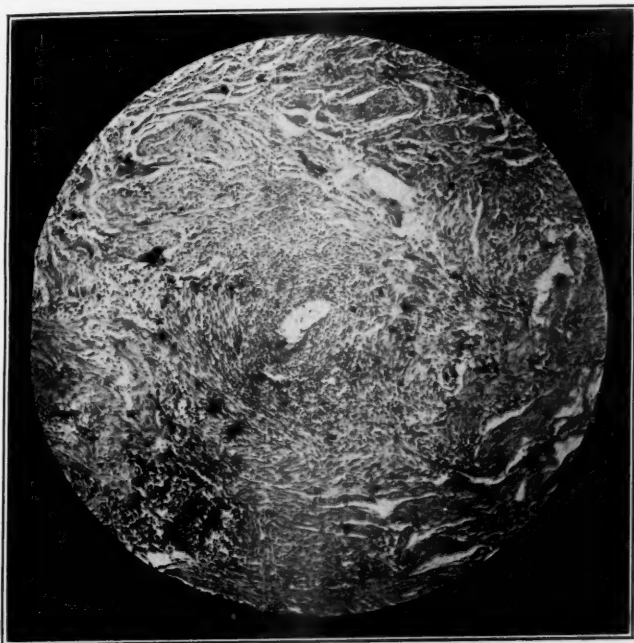


Fig. 7.—Case 95. Endometrial implant in wall of tube-uterine end; glands grow fewer as the tissue is followed and lie farther away from serous surface.

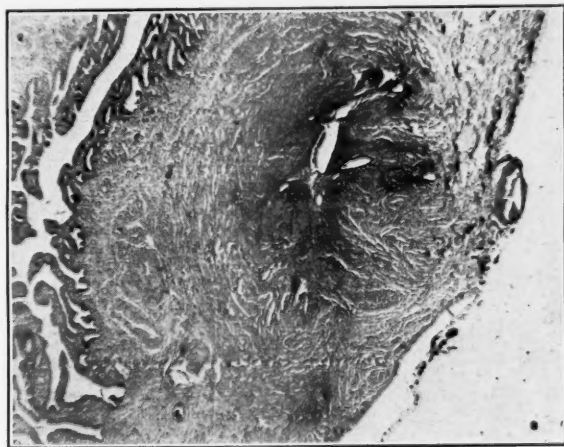


Fig. 8.—Case 95. Endometrial implant in wall of tube; low power view of Fig. 5.

Thus, logically, we can trace the steps that led us to our conclusions:

1. Endometrial tissue was found lying free in the tubal lumen and could have originated only in the uterine cavity.

2. Endometrial tissue was found imbedded in the tubal wall and its proximity to the serous surface of the tube suggests that it was a serous surface implantation originally.

3. Endometrial glands were found in the decidua of an ectopic pregnancy, definitely identifying it as decidual change of endometrial tissue, not as a possible decidual reaction of tubal wall elements. Time does not permit, nor is it necessary here, to quote Sampson's<sup>5, 6</sup> linking of the above phenomena into a chain of evidence to prove how endometrial implants occur and that their origin is from detached shreds of endometrial tissue, or Jacobson's<sup>7-10</sup> work, showing that such fragments are able to implant and grow in other locations after their detachment.

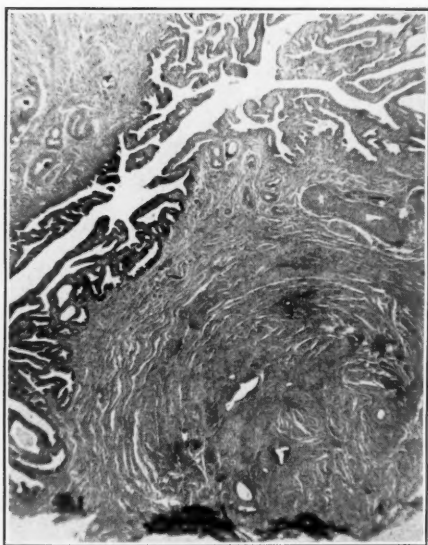


Fig. 9.



Fig. 10.

Fig. 9.—Low power view of Fig. 6.

Fig. 10.—Low power view of Fig. 7.

4. Decidual tissue was not found in two cases of the series of 16 tubal pregnancies because of the wide destruction of the tissues by hemorrhage, but was found in the other 14 cases where the anatomy was not disrupted.

Endometrium is tissue with a specialized function, but its structure is simple and less differentiated than other body tissues. Novak says that the glands are simple tubules and that the stroma is simple labile embryonic connective tissue. Its lack of differentiation enables it to assume readily the wide range of changes it is forced to go through in response to hormonal influences and to regenerate speedily after most extensive denudation, and also accounts for its ability to form endometrial implants.

The endometrium offers the only possible nidus for the embryo and exists only for that purpose. This implies the existence of a bond, an affinity and a positive chemotactic attraction on the part of the mobile

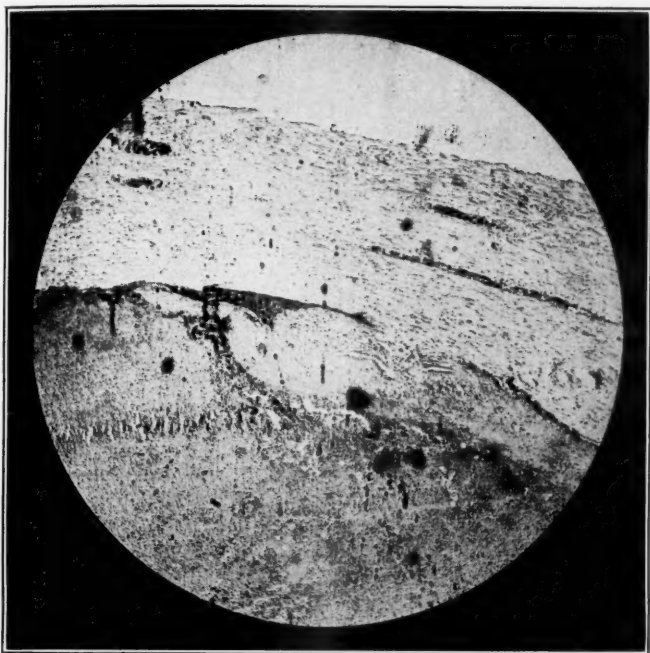


Fig. 11.—Decidual tissue, containing endometrial glands, in wall of tube the site of ectopic gestation.

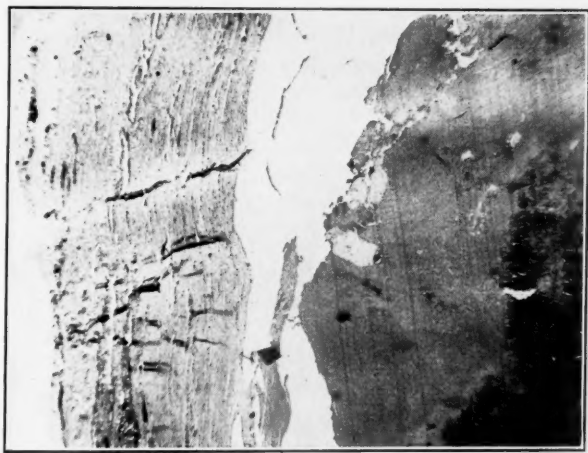


Fig. 12.—Low power view of Fig. 11.

zygote which at this stage behaves like any of the protozoa and possesses the general properties common to all protoplasm, including definite reaction to stimuli, repulsion from unfavorable stimuli, attraction to



favorable ones. This, we believe, is the decisive element in the implantation of the fertilized ovum. It appears to us a logical assumption as reasonable as the assumption that the spermatozoon is attracted to the ovum. It has been shown that the plasmodial trophoblast imparts to the zygote a certain degree of motility.

For these latter assumptions we have no definite proof, but we believe them to be correct; they become convictions on consideration of the evidence we have been able to accumulate.

#### CONSIDERATION OF THE LITERATURE

The finding of decidual tissue in ectopic locations is not new. As far back as 1897 Webster<sup>11</sup> described decidual tissue in tubal pregnancy. In 1904<sup>12</sup> he reported a case of ovarian pregnancy and mentioned the finding of decidua-like cells on the surface of the ovary and that Schmori had observed the same. He found these decidua-like cells in uterine pregnancy in other sites of the pelvic peritoneum—the places that Cullen taught us to look for adenomyosis and Sampson for endometriomas. But he believed that the tube could and did produce a decidual reaction when pregnancy occurred (even intra-uterum) because genetically it arose from müllerian tissue like the uterus.

In 1931 Weiss<sup>13</sup> reported finding endometrium in five fallopian tubes, one a pre-gravid stage, premenstrual in another and quoted cases reported by others, 2 by Schridde and Schonholz, one by Hohnes (in which the endometrium was found in the intramural part of the tube) one by Schwarz and Crossen, one by Schindler, one by Szamek (endometrium in the right and left tubes), one by R. Meyer demonstrating functioning endometrium in the tube.

Osiakina and Schmatok<sup>14</sup> in 1933 found a decidual reaction in the tube in 21 per cent of a series of 21 tubal pregnancies independent of the localization of the implanted ovum.

Frank<sup>15</sup> says that decidual formation in the tube is imperfect and is limited to a few tubal folds. Kermauner<sup>16</sup> found decidua in 15 per cent of cases. Litzenberg<sup>17</sup> says that though decidual reaction can sometimes be found in pregnant tubes, it is limited to only a few cells and a true decidual basalis is never present. Like many others he believes that it is the tubal mucosa that undergoes the decidual change due to the presence of the chorionic villi. With this view, however, we cannot agree for all evidence is against it. But the paucity of decidual tissue to be found we have to admit. But this is due to the small size of the primary endometrial implants. If the endometrial tissue were sufficiently large, all cases of ectopic pregnancy would go on developing at least until the fetus had reached full development, and no tubal ruptures would ever occur. There is universal agreement that the decidua has a two-fold action, affording on one hand a nearly perfect bed for the embryo, on the other preventing, by the formation of the fibrin layer of Nitabusch, wild uncontrolled invasion by the chorionic villi. No other tissue can resist this penetration and continue to harbor the zygote. In ectopic pregnancy it is the scantiness of the barrier that causes the tubal rupture and the death of the embryo, because as soon as the villi invade extradecidual tissue, coagulation of the blood in the sinuses occurs and the embryo has committed suicide. This brings up the question of secondary abdominal pregnancy.

#### SECONDARY ABDOMINAL PREGNANCY

It has been quoted repeatedly in textbooks and elsewhere as indubitable, that a tubal pregnancy may lose its position in the tube and



implant itself secondarily elsewhere continuing its growth in the new site. But such a view is hardly tenable, for it is evident that the embryo depends upon the maintenance of a free flow of maternal blood around its chorionic villi. When the trophoblast is confined in decidua, the embryo is nourished, but when the villi break their bounds, they become imbedded in blood clot and the embryo is in a short while asphyxiated. How can secondary abdominal or intraligamentous pregnancy then occur? It is manifestly impossible for an embryo once surrounded by coagulated blood to extricate itself when deposited in a fresh place and recommence its development. Whether tubal rupture or tubal abortion occur the fate of the embryo is sealed from the moment the perifetal coagulation starts. Hence the existence of an ovarian pregnancy, an abdominal pregnancy, or an intraligamentous pregnancy cannot follow on its extrusion from the tube but exists because it begins its development primarily in these sites.

#### SUMMARY

Various observers including ourselves, have demonstrated healthy endometrial tissue in tubal lumina. Sampson and Jacobsen, and others have proved beyond doubt that such endometrial tissue can and does implant itself and grow elsewhere displaying a preference for serous surfaces. Cases have been reported in the literature of endometrial tissue in the tubes. We have one such case.

Many observers have found decidual tissue in tubes whether or not they were the site of pregnancy. We have found it present at the site of the pregnancy in 62 per cent of casual specimens, in 87½ per cent of cases where we made a careful search and believe that it is present at the outset in 100 per cent of cases.

In one case we succeeded in finding endometrial glands in this decidual tissue, proving that the decidual reaction was caused by the response of endometrial elements and not the tubal structure itself. The fact that the fibrin layer of Nitabusch can be demonstrated in these ectopic decidual tissues shows that the ectopic endometrium carries out its functions as completely as when it was on the uterine wall.

The ectopic endometrial tissue was found in 1 out of 204 cases, an incidence of ½ per cent. The ratio of ectopic to intrauterine pregnancy is about 1 to 202 (Schumann's<sup>18</sup> series) in Farrar's<sup>19</sup> series 4 to 309, a significant correspondence of statistics and the explanation of the frequency of ectopic gestation.

#### CONCLUSIONS

1. All ectopic pregnancies, tubal or otherwise, occur because of nidation of the fertilized ovum in a locus of ectopic endometrial tissue to which the ovum is chemotactically attracted.

2. The fate of the gestation depends upon the amount of endometrial tissue present to undergo the decidual reaction and upon the depth of penetration of the ovum beyond the borders of this decidua.

3. All ectopic pregnancies are primary.

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### A HISTOLOGIC METHOD FOR THE EARLY DIAGNOSIS OF PREGNANCY

BERTRAM G. SMITH, PH.D., AND ENDRE K. BRUNNER, M.D.,  
NEW YORK, N. Y.

(From the Departments of Anatomy and Gynecology, College of Medicine, New York University)

#### INTRODUCTION

IN A PREVIOUS article (Smith and Brunner, 1934) we described a modification of the typical structure of the human vaginal epithelium which, we thought, might be of practical importance in the early diagnosis of pregnancy. Subsequently, we have examined this question with the advantage of much additional material. The results of this study are set forth in the present paper.

In order to recognize any peculiarities of the vaginal epithelium associated with pregnancy, one must be familiar with the normal structure during the menstrual cycle. Also, one must be able to recognize the common pathologic modifications of the vaginal mucosa, modifications which, in some cases, make this method of diagnosis inapplicable. Since this background is supplied by our previous paper, brief descriptions will suffice here.

#### MATERIAL AND METHODS

All the material considered in the present paper was obtained by the method of biopsy. Very small pieces, seldom exceeding 3 mm. in diameter, of the vaginal mucosa were excised from women who, with few exceptions, were patients in the gynecologic clinic. The vagina is a relatively insensitive organ and the pain connected with the biopsy-taking so slight and brief that many patients never complained of it. Anesthesia was never used. After the introduction of a bivalve

speculum a prominent mucosal fold was selected and punched with a Myle's cutting-edge fenestrated forceps. Upon withdrawal of the speculum, the folds of mucosa closed over and the minute wound collapsed leaving no bleeding surface. The slight wounds thus protected healed readily. The pieces were fixed in 10 per cent formalin, passed directly to 80 per cent alcohol and subsequently imbedded in paraffin. Serial sections were cut with a thickness of  $10\mu$  and stained with Delafield's hematoxylin followed by eosin.

In cases where the surface of the epithelium was folded, care was taken to orient the object so that sections would be cut transverse to the principal fold. Notwithstanding this care in orientation, some sections or portions of sections were found to be oblique. Such sections are misleading in that they tend to give an exaggerated idea of the size of cells that are more or less flattened. In the diagnosis of pregnancy, it is important to avoid oblique sections. Even a small amount of obliquity can be detected if the section cuts through some slender papillae.

The material for this investigation consists primarily of 155 biopsies from 79 cases of pregnancy and suspected pregnancy. Most of these biopsies are normal, but some are pathologic. The ages of the patients range from sixteen to forty-two

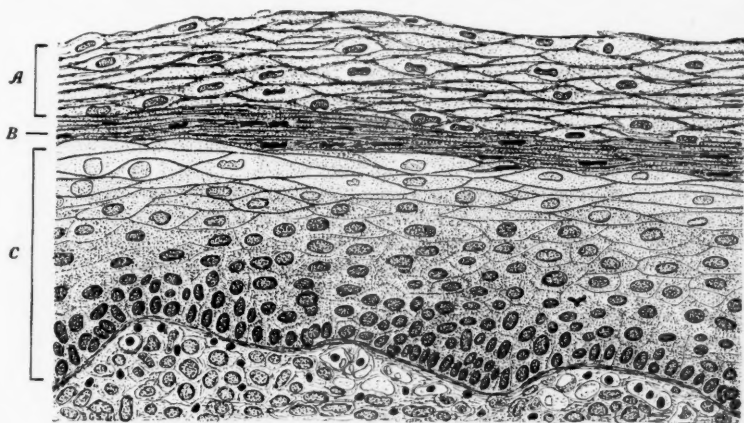


Fig. 1.—Drawing of a transverse section through the vaginal mucosa of a twenty-three-year-old nullipara, showing a portion of the epithelium overlying the summit of a papilla.  $\times 540$ . A, Superficial zone; B, middle zone or intraepithelial zone of cornification; C, basal zone. (After Smith and Brunner, 1934, *Am. J. Anat.*)

years. We have for comparison 118 normal biopsies from 49 women representing every phase of the menstrual cycle, also 41 pathologic biopsies from 19 women in various phases of the menstrual cycle. This material has been fully described in our previous paper, but will receive some attention here.

All the photomicrographs illustrating this article were made by Mr. Martin Haggett, using the same optical equipment throughout. The photographs were taken with a magnification of  $\times 130$ , and in the process of reproduction were reduced to  $\times 100$ .

#### TYPICAL STRUCTURE OF THE VAGINAL MUCOSA

The epithelium of the human vagina (Fig. 1) may be divided into three sharply defined zones or strata, as follows: (1) A superficial zone composed of moderately flattened cells that stain faintly with hematoxylin and eosin. (2) A middle zone, the intraepithelial zone of corni-

fication, in which the cells are very flat and stain deeply. (3) A basal zone in which the structure is much the same as in the stratum germinativum or malpighian layer of the epidermis. The basal zone is comparatively thick and shows a gradation in the character of its cells as one proceeds from the basement membrane toward the periphery. Roughly,

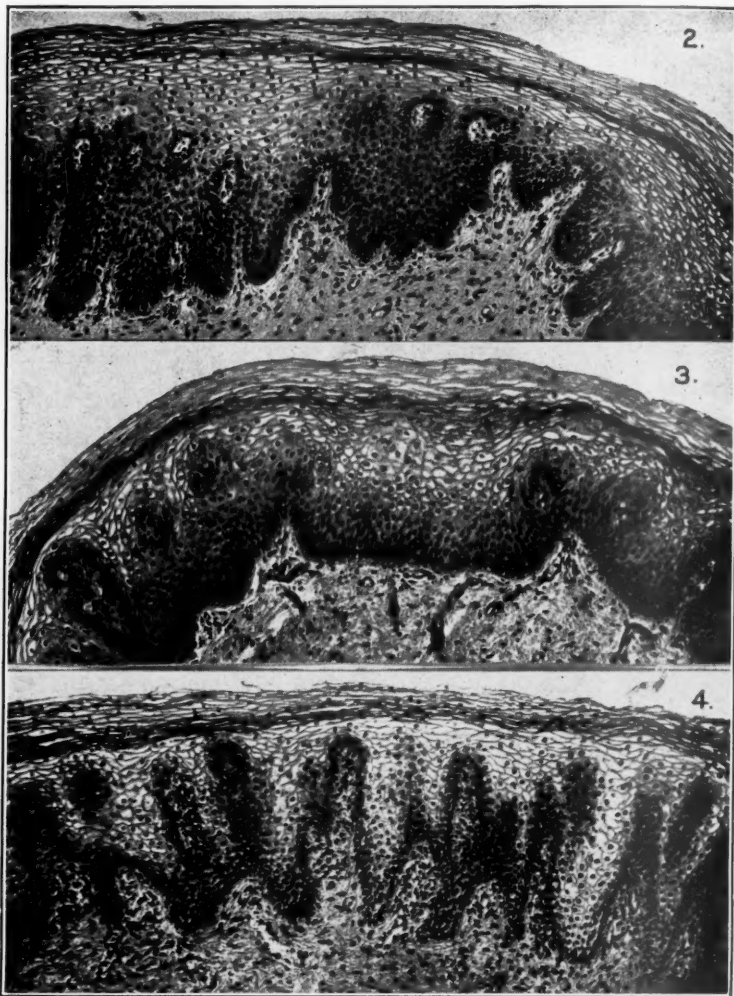


Plate I. Photomicrographs of sections of the vaginal mucosa in women with normal menstrual cycles, in the absence of pregnancy.  $\times 100$ . (After Smith and Brunner, 1934, *Am. J. Anat.*)

Fig. 2.—This section shows less than the usual amount of vacuolation in cells of the basal layer of the epithelium.

Fig. 3.—The amount of vacuolation here shown approximates the average.

Fig. 4.—The amount of vacuolation is a little above the average.

this zone may be subdivided into three layers: (a) A deep zone appearing, in sections, as a few rows of small cells in which the nuclei stain deeply. Cells of the row immediately adjoining the basement membrane

are usually columnar; the others are cuboidal or polyhedral. (b) A zone of rather large polyhedral or slightly flattened cells that stain moderately. (c) A zone of clear, slightly flattened, highly vacuolated cells that stain faintly. Peripherally, this zone is sharply bounded by the zone of intraepithelial cornification.

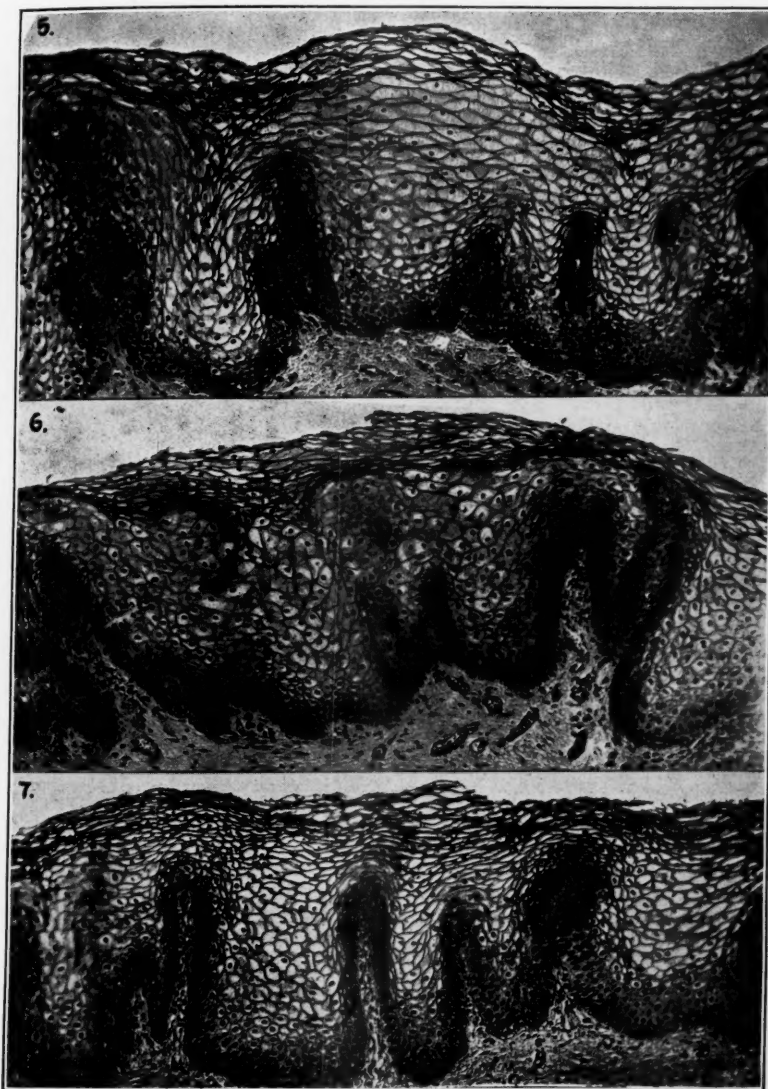


Plate II. Photomicrographs of sections of the human vaginal mucosa in early stages of pregnancy.  $\times 100$ .

Fig. 5.—Approximately three weeks pregnant (menstrual flow six days overdue). The amount of vacuolation is slightly above the average for the first month.

Fig. 6.—Approximately six weeks pregnant (menstruation thirty-two days overdue). The amount of vacuolation is above the average for the second month.

Fig. 7.—Approximately eight weeks pregnant (menstruation forty-five days overdue). The amount of vacuolation is only slightly above the average for the second and third months.



Even in normal mucosae, a considerable number of extravascular white blood corpuscles, usually lymphocytes, may be found in the layer of delicate connective tissue (lamina propria) underlying the basement membrane of the epithelium. These are shown as large black dots in Fig. 1. A slight amount of infiltration of leucocytes into the basal layer of the epithelium is a normal occurrence. In Fig. 1 only a single leucocyte, with distorted nucleus, is shown imbedded in the epithelium; but in an epithelial area of the size represented in the drawing, there would ordinarily be several leucocytes. The lamina propria contains numerous small blood vessels and small lymphatic vessels.

The structure thus described is fundamental, and in normal cases there are no essential differences when different regions of the same vaginal mucosa are compared. Nevertheless, the picture varies considerably depending on the presence or absence of papillae. Where papillae are absent throughout areas of considerable extent, the stratification is fairly uniform; where they are numerous, as shown in most of the figures illustrating this paper, the basal zone is much thicker between the papillae. This increased thickness is due to an increase in the number of clear cells and polyhedral cells. Differences correlated with the phases of the menstrual cycle are slight and need not concern us here. When normal mucosae from different individuals are compared, the chief differences are those relating to the degree of development of the intraepithelial zone of cornification and to the number and size of the clear cells. We are here concerned mainly with the clear cells, since the cells of the clear zone are especially large and numerous during pregnancy.

We have previously studied the clear cells in 118 normal biopsies from 49 women in various phases of the menstrual cycle (Smith and Brunner, 1934). After a preliminary examination of these biopsies to determine the largest amount of vacuolation present in any of them, all were graded with respect to the amount of vacuolation, on a scale of five. (In the present paper, Grade 1 is illustrated by Fig. 2; Grade 2 by Fig. 3; and Grade 3 by Fig. 4). The average for the 118 biopsies is 2.41. In the entire series, Grade 5 was assigned to only seven biopsies from five patients. Since Grade 5 is rare, it may be due to the operation of some unusual factor. It is possible that the five patients were in a very early stage of pregnancy. All the dates for the seven biopsies fall within twenty-six days of the beginning of the preceding menstrual flow, but we do not know whether the supposed cycles were terminated by menstruation.

#### PATHOLOGIC MODIFICATIONS

In normal material taken at any stage of the menstrual cycle, there is considerable variation in the number and size of the clear cells in different individuals (Figs. 2 to 4), but the clear zone is always present. In



cases of chronic vaginitis the formation of the clear zone is partially or wholly suppressed, save that one may occasionally find normal areas in which the clear zone is well developed. Since even a moderate degree of inflammation is sufficient to prevent the increase in size and number of the clear cells characteristic of pregnancy, it is important to be able to recognize the other structural modifications associated with vaginitis.

In mild vaginitis, of whatever origin, there is moderate hyperemia with little or no extravasation of blood, more than the usual number of leucocytes in the tunica propria, marked infiltration of leucocytes into the basal layer of the epithelium, and a blurring of the boundaries of the polyhedral cells. The layer of clear cells, the zone of cornification and the superficial zone appear almost normal. In moderate or severe vaginitis of a chronic nature, the histologic modifications extend to the zone of cornification and even to the superficial zone. Nevertheless, one may find localities where the structure is almost normal, while in other portions of the same biopsy, or in other biopsies from the same mucosa, the pathologic modifications are quite obvious. We shall now describe the usual effects of chronic inflammation on the structure of the vaginal mucosa, layer by layer.

In many instances the superficial zone tends to resemble the zone of cornification. In severe cases the superficial zone is dense and its cells are greatly flattened; it undergoes desquamation in scalelike masses of cells, and may be entirely lacking (in sections). The zone of cornification is usually thicker and is always denser than in its normal state; it may be almost homogeneous. This is often the most striking indication of chronic vaginitis. In all cases the layer of clear cells suffers reduction in some degree. In severe cases there is not only entire absence of clear cells, but there is a reduction in the number and size of the pale, slightly vacuolated cells that normally underlie the clear cells. The layer of polyhedral cells is unusually dense and may extend quite to the zone of cornification. Somewhat rarely, the layer of clear cells is replaced by a stratum granulosum.

Characteristically, there is a decided increase in the number of leucocytes in the lamina propria, especially in the papillae, and a corresponding increase in the amount of infiltration of leucocytes into the basal layer of the epithelium. Nevertheless one may find, in a portion of the mucosa where the number of leucocytes is not excessive, all the other modifications characteristic of chronic vaginitis.

Usually, the blood vessels are distended and there is some extravasation of blood into the connective tissue. Caution is needed in interpreting this as evidence of hyperemia, for it may be an artifact. In many cases the extravasated blood within a papilla crowds the other tissues aside, forming a small hematocoele with a sharply defined spherical boundary. This enlarges at the expense of the epithelium, and in extreme cases may extend almost to the periphery.

## THE VAGINAL MUCOSA IN PREGNANCY

In our previous investigation (Smith and Brunner, 1934) we were impressed by the increase in vacuolation of the cells of the distal portion of the basal zone during pregnancy. Not only do the clear cells increase in size, but the clear zone extends almost to the deep layer of darkly staining cells (as in Figs. 5 to 7 of the present paper). This increase did not occur in material that was obviously pathologic. Our normal material taken during pregnancy consisted of 48 biopsies from 20 pregnancies ranging in duration from approximately three weeks to the eighth lunar month inclusive. In order to facilitate comparisons, we attempted to grade these biopsies with respect to the amount of vacuolation in the basal layer, using the scale employed for the study of vacuolation during the menstrual cycle. It was necessary to increase the range of this scale from five to six, in order to make it applicable to all biopsies taken during pregnancy. (In the present paper, Grade 6 is illustrated by Figs. 5 to 7, though the amount of vacuolation shown in Fig. 7 is barely sufficient to justify a grade higher than five.) The general average for the 48 biopsies from 20 pregnancies was 4.96, which should be compared with the general average of 2.41 for 118 normal biopsies from 49 women in various phases of the menstrual cycle.

In what follows, all biopsies obtained during our earlier study of pregnancy are incorporated with our later material. At present, our material consists of 155 biopsies from 79 cases of pregnancy and suspected pregnancy. Of these, 33 biopsies from 26 patients are obviously pathologic and of no value for diagnosis. The fact that the amount of vacuolation in these specimens is small (in some instances clear cells are entirely absent) should not be interpreted as negative evidence; for, as previously explained, even a moderate inflammation usually inhibits vacuolation. Nevertheless, from nine of these patients partially normal biopsies also were obtained; these are included in the normal group to be described presently. Thus, out of 79 patients, 17, or 21.5 per cent, furnished exclusively pathologic biopsies. Of this group 12 patients (one ectopic pregnancy) were definitely pregnant, 2 were not pregnant, and 3 remained doubtful since the clinical evidence was inconclusive and the patients did not return for reexamination. The ages of these patients ranged from seventeen to forty-two years.

There remain for consideration 122 normal or nearly normal biopsies from 62 cases of pregnancy and suspected pregnancy. The ages of these patients range from sixteen to forty-one years. In estimating the duration of pregnancy, the twelfth day of the menstrual cycle is taken as the most probable date of conception. On this basis, every lunar month of pregnancy excepting the tenth is represented in the biopsies. In the earliest case of suspected pregnancy, menstruation was one day overdue. There are 18 cases where menstruation was not more than twelve

days overdue; according to the mode of reckoning employed, these fall within the first month. There are 24 cases for the second month. Thus, 67 per cent or about two-thirds of the total number of cases from which normal biopsies were obtained fall within the first two months of pregnancy or suspected pregnancy.

In 7 cases of suspected pregnancy, with menstruation from one to seventeen days overdue, the histologic diagnosis was negative. These cases were represented by 10 biopsies. At later clinical examinations six of these patients were found not pregnant; the other patient did not return. In a single patient (thirty-eight years of age, menstruation forty days overdue) the histologic diagnosis based on two biopsies was doubtful. Seven weeks later, this patient was reported not pregnant.

In 54 cases, represented by 110 biopsies, the histologic diagnosis was positive. In 47 of these cases a clinical diagnosis of pregnancy was made at the time of biopsy; in the remaining 7 cases, pregnancy was merely suspected. Since approximately two-thirds of the 54 cases fall within the first two months of pregnancy, it is important to note any evidence obtained from later clinical examinations. In 14 cases, menstruation was from six to twelve days overdue; these cases are assigned to the first month of pregnancy. Ten of these patients were examined at a later date and pronounced pregnant; the other 4 did not return. In 20 cases menstruation was from thirteen to forty days overdue; these cases are assigned to the second month of pregnancy. Of this group, 8 patients returned for examination and were pronounced pregnant; the others did not return. Of the remaining 20 patients, in later stages of pregnancy, only five returned for examination and in these cases the diagnosis of pregnancy was confirmed. Thus, all the clinical evidence available supports the histologic diagnosis of pregnancy.

It is of interest to note that a histologic diagnosis is possible in a very early stage of pregnancy. In 4 cases a positive diagnosis was made when menstruation was only six days overdue; in 2 of these cases the diagnosis was confirmed by a later clinical examination. In 2 cases a positive diagnosis was made when menstruation was eight days overdue; both diagnoses were confirmed by later clinical examinations. In one of the latter cases there was a history of a single intercourse three weeks before the biopsy was taken.

Some comparisons with biopsies taken during the menstrual cycle are in order. In all the biopsies taken during pregnancy or suspected pregnancy, the amount of vacuolation in the basal layer of the epithelium was graded on a scale of six. In the 110 biopsies from 54 cases in which the histologic diagnosis was positive, the average amount of vacuolation is 4.98. The general average for the menstrual cycle is 2.41; this is based on 118 normal biopsies, well distributed throughout the men-

strual cycle, from 49 patients. Thus it appears that the amount of vacuolation is approximately twice as great during pregnancy.

It is known that the epithelium of the vaginal mucosa is normally rich in glycogen. In thirty women with normal menstrual cycles and normal vaginal mucosae, Niderehe (1923) found the glycogen content highest during the premenstrual stage. On the other hand, Gisbertz (1929 and 1930) found great variation in the glycogen content, but concluded that the variations were not cyclical in character. Gisbertz believes that the intracellular vacuoles visible in ordinary preparations of the vaginal epithelium are filled, during life, with glycogen in liquid form. Our own studies (Smith and Brunner, 1934) indicate that variations in the amount of glycogen are not related to the menstrual cycle.

Niderehe (1923) stated that there is an increase in the amount of glycogen during the early stages of pregnancy, and a gradual decrease during the later months. It would be interesting to know if the same rule holds for vacuolation. Using our 110 normal or nearly normal biopsies from 54 patients with a histologic diagnosis of pregnancy, we computed the average amount of vacuolation for each lunar month represented. The results are shown in Table I. The slight drop in vacuolation indi-

TABLE I. AVERAGE AMOUNT OF VACUOLATION IN CELLS OF THE BASAL ZONE OF THE VAGINAL EPITHELIUM FOR EACH OF THE FIRST NINE LUNAR MONTHS OF PREGNANCY. BASED ON 110 BIOPSIES FROM 54 WOMEN.  
THE GENERAL AVERAGE IS 4.98

LUNAR MONTH	1	2	3	4	5	6	7	8	9
No. of patients	14	20	9	6	1	1	1	1	1
No. of biopsies	25	39	19	13	7	3	1	1	2
Vacuolation	5.48	4.82	4.84	5.00	5.00	5.33	5	5	5

cated for the second month may be significant, and there is no change during the third month; but in the later months the number of cases is too small to be of much use in this connection. Lewis (1935) described and illustrated (photographically) a high degree of vacuolation of the vaginal epithelium at the very end of pregnancy, the time of delivery.

#### DISCUSSION

The principal defect in our method for the diagnosis of pregnancy is that it is not applicable to cases exhibiting marked pathologic modifications of the vaginal mucosa. In chronic vaginitis, the formation of intracellular vacuoles, upon which the histologic method of diagnosis depends, is inhibited. For this reason, in about one-fifth of our cases a diagnosis by this method was impossible. It is probable that in private practice the proportion of pathologic cases would be lower.

It is pertinent to consider some other conditions that might make a histologic diagnosis difficult or impossible. In our previous contribution

(Smith and Brunner, 1934) we stated that in pathologic amenorrhea (represented by 19 otherwise normal biopsies from 5 patients), the amount of vacuolation is greater than during the menstrual cycle, but decidedly less than during pregnancy. The number of cases is too small to enable an unqualified conclusion to be drawn. We can see no reason why vacuolation should be increased during pathologic amenorrhea. Nevertheless, in view of the facts stated it seems possible that in occasional cases of pathologic amenorrhea the amount of vacuolation might be large enough to be confusing.

We have stated (Smith and Brunner, 1934) that during and after the menopause the distal portion of the basal zone (in 7 fairly normal biopsies from 7 patients) is rather highly vacuolated, but we were careful to add: "Niderehe (1923) states that after the menopause there is a decrease in the amount of glycogen associated with a lessened height of the vaginal epithelium. We do not know whether the intracellular vacuoles found in our sections represent spaces filled, during life, with glycogen, but the cytological appearance is not quite the same as it is during the child-bearing period." This important qualification appears to have been overlooked by Lewis (1935) in his references to our article. Perhaps we should be more explicit. We are by no means assured that the vacuolation found after the menopause is entirely homologous with that present during the menstrual cycle and during pregnancy. It seems, in part, to be a consequence of involution—a result of the increasing poverty of cytoplasm accompanied by an actual decrease in secretory function. Better fixation and the use of special stains are needed to settle this question.

When, in 1929, we began our studies on the structure of the vaginal mucosa, it was in search of a method for the diagnosis of pregnancy. Meanwhile, other tests for pregnancy have come into general use. This should not entirely preclude the use of the method here described. For various reasons, it is well to have several methods available. As compared with the Aschheim-Zondek and the Friedman tests, the histologic method has the advantage of rapidity. The biopsies are small and the usual paraffin technic can be speeded up so that the sections are ready for study in a very few hours. We hope that some one will test this method in a sufficient number of cases of ectopic pregnancy, where the time factor is important.

In this paper considerable attention has been given to conditions that may defeat an attempt at a histologic diagnosis. This should not obscure the fact that, in normal cases, the method is almost uniformly successful. Often, a single glance at a preparation under the low power of the microscope enables one to make an unqualified decision. However,



we would emphasize the advantage of preparing an entire series of sections of each biopsy; for in mucosae that are mainly pathologic, normal areas may sometimes be found.

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## CIRCULATION TIME STUDIES IN PREGNANT WOMEN

NATHAN M. GREENSTEIN, M.D., AND JACOB CLAHR, M.D.,  
NEW YORK, N. Y.

(From the Department of Obstetrics, Morrisania City Hospital)

OUR purpose in reporting circulation time studies in pregnancy is to supply additional data relative to the changes which occur during normal gestation.

It has been generally accepted that during normal pregnancy the work of the heart is increased. This is evidenced by an increase in minute volume output of the heart, increase in circulating blood volume, increase in basal metabolic rate, increase in ventilation and diminution in vital capacity.

Lindhard,<sup>1</sup> Stander and Cadden,<sup>2</sup> Haupt,<sup>3</sup> Schmidt,<sup>4</sup> Schroeder,<sup>5</sup> Anthony and Hansen<sup>6</sup> have shown that the minute volume output of the heart increases, from a minimum of 15 per cent to a maximum of 74 per cent from the fourth month of pregnancy onward. The increase in cardiac output is due to increased venous return and greater diastolic filling of the auricles. In accordance with Starling's law, the increased venous return causes a greater stretching of the heart muscle during diastole, and a consequently greater stroke volume output.

In addition to the increased venous return, Dieckmann and Wegner,<sup>7</sup> Schoenholz,<sup>8</sup> and others have shown an increase in the volume of circulating blood, with an increase in plasma, a relative or absolute diminution in the number of formed elements, and a relative anemia.

Plass and Yoakum<sup>9</sup> have shown a progressive increase in the basal metabolic rate from the fourth month of gestation to term and a subsequent fall during the puerperium. Boothby and Plummer<sup>10</sup> have shown that there is a greater amount of energy expended per unit of work in those with elevated basal metabolic rates than in those with normal rates.

Krukenberg<sup>11</sup> showed that following a measured amount of work, the blood pressure in pregnant women rose higher than in nonpregnant women, and was slower in returning to normal. The pulse rates of the pregnant women were more rapid than could be accounted for by the increase in work.

The ventilation rate has been shown by Eismayer and Pohl<sup>12</sup> to be increased, while the vital capacity is diminished. They also found a slight elevation of pulse and blood pressure in pregnancy.



Dyspnea on exertion and easy fatigability, the early symptoms of cardiac decompensation, are of frequent occurrence. Signs of cardiac disturbance, such as tachycardia, premature contractions, and even transient auricular fibrillation may occur in normal pregnancy.

These findings would all seem to corroborate the concept that the heart works harder and less efficiently in pregnancy.

We felt that if the heart did perform less efficiently, this might be reflected in the progressive prolongation of the circulation time during the course of pregnancy. Blumgart<sup>13</sup> showed that there is a definite correlation between speed of circulation and functional capacity of the heart.

The determination of the speed of circulation by the introduction of a foreign substance into the blood stream at one point, detecting its presence at another, and measuring the elapsed interval is a procedure that has been known for many years.

Blumgart<sup>14</sup> has summarized completely the various methods employed, and with the use of radioactive substance revealed the great value of this method in studying the circulation in normal and abnormal states.

Harrison's<sup>15</sup> careful studies have shown that in a failing myocardium, symptoms and signs are due to "backward failure" which results in an accumulation of blood in the lungs from left heart weakness, or congestion of the liver and peripheral edema in right heart failure. Such slowing of the circulation would tend to slow up any foreign substance present in the blood stream.

Despite any symptoms of cardiac weakness, such as dyspnea and easy fatigability, the finding of a normal circulation time effectively rules out the presence of cardiac failure. It is possible by circulation time studies to determine not only the efficiency of the whole heart, but also of the right and left components.

We have selected the method devised by Fishberg, Hitzig and King<sup>16</sup> for our determinations. It is true that the method is not entirely objective, but Hitzig<sup>17</sup> has shown that though the time may vary from one individual to another there is very little change in the same individual. He found that repeated tests in 22 cases showed a variation of 0.5 to 2.0 seconds. Consequently, we may accept this test to be quite accurate.

#### PROCEDURE

With the patient at rest for at least one-half hour, a solution of 3 gm. of saccharine (gluside) is dissolved in 3 c.c. of sterile distilled water, and then injected rapidly into the ante-cubital vein through an 18-gauge needle. The patient has been instructed to announce when a sweet taste is first detected at the base of the tongue. Timing begins from the first drop injected. This is the arm-tongue time and measures the passage of blood through the right and left sides of the heart.

With the needle in situ, the syringe is removed and replaced by one containing 3 c.c. of a freshly prepared 10 per cent solution of ether in sterile distilled water. The patient is instructed to exhale forcefully, and the solution is rapidly injected. The time is measured from the beginning of the injection until the moment when

the examiner detects the odor of ether. This measures the arm-lung time or the passage of blood through the right heart as far as the arterial capillaries of the lung.

Normal figures for the tests in nonpregnant women are as follows: from eight to sixteen seconds for arm-tongue time, and four to eight seconds for arm-lung time.

For subjects we selected thirteen normal pregnant women from the Morrisania City Hospital antepartum clinic. At monthly intervals, beginning as early as the third to the fifth month of gestation, we did arm-lung and arm-tongue determinations. Blood pressure and pulse rates were taken, urinalyses and physical examinations were done at the same time. Both multiparas and primiparas were included. We feel that there is no danger in this procedure. Fishberg, speaking before the Section of Medicine at the New York Academy of Medicine, stated that several hundred such determinations have been made with no untoward effects. In our series of 52 arm-tongue and 58 arm-lung determinations, only on three occasions did thrombosis of the antecubital vein occur. There were no other complications.

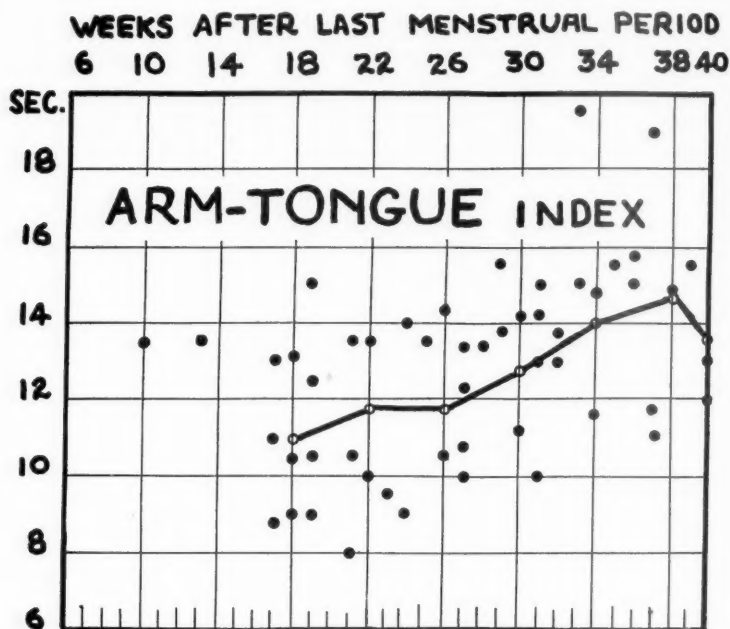


Chart 1.

#### RESULTS

There were 52 determinations of arm-tongue time done on 13 patients (Table I). The minimum time was eight seconds in the twenty-first week of gestation and the maximum was 19.4 seconds in the thirty-third week. All patients except Cases 2 and 8 showed an increase in the circulation time as gestation progressed. There was only 1 determination in Case 2. Chart 1 contains all the arm-tongue determinations represented by black dots, with the average for each month represented by a circle. The average arm-tongue time shows a progressive increase, from 10.9 seconds at the eighteenth week of gestation until it reaches a maximum of 14.7 seconds at the thirty-eighth week of gestation. There is a drop to 13.5 seconds at the fortieth week of gestation.

There were 58 determinations of arm-lung time on the same 13 patients (Table I). The minimum time was 2.8 seconds obtained in the seventeenth and twenty-sixth

weeks of gestation. The maximum time was 6.8 seconds obtained in the eighteenth, nineteenth, twenty-second, twenty-fifth, thirty-third, thirty-fifth, and thirty-seventh weeks of gestation. All patients except Cases 4, 7, and 8 showed an increase in the arm-lung time as gestation progressed. Chart 2 contains all the arm-lung determinations represented by black dots, with the average time for each month represented by circles. With the exception of a slight drop of 0.5 second at the twenty-second week of gestation, there is a progressive increase in the average time. Beginning with 3.9 seconds at the eighteenth week of gestation the arm-lung time increases to 5.4 seconds at the fortieth week.

It is apparent, then, that there is a slight but definite slowing of the velocity of blood flow through the lungs. Despite the increase in arm-tongue and arm-lung times, however, these times are still within normal limits. This is in contrast to the findings of Klee.<sup>18</sup> He used Koch's<sup>19</sup> fluorescein method, where the normal average circulation time is 20.8 seconds. He found in normal primiparas and multiparas

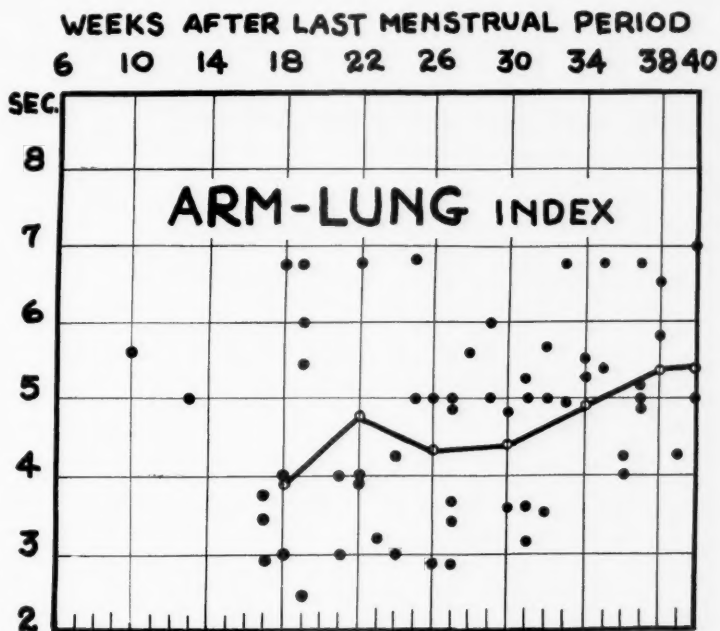


Chart 2.

increases over the normal ranging from 2.6 seconds to 6.4 seconds, in the last three months of gestation. However, we found, as he did, a slight decrease in time in the last two weeks of pregnancy. He ascribed this decrease to the lowering of the diaphragm with the descent of the fetus into the pelvis, allowing for greater thoracic space and better circulation. Spitzer<sup>20</sup> used the decholin method of Winternitz, Deutsch, and Brüll,<sup>21</sup> which is similar to the saccharin method we employed. He found increases in circulation time during the latter part of pregnancy, but he did not follow his cases from month to month.

#### DISCUSSION

Blumgart<sup>22</sup> showed that the greatest part of the time required for the blood to pass from the antecubital vein through the right and left sides of the heart is consumed in the lung capillaries, the other com-

TABLE I

CASE	PARITY	PERIOD OF GESTATION IN WEEKS	CIRCULATION TIME IN SECONDS	
			ARM-TONGUE	ARM-LUNG
1	iv	10	13.6	5.6
		19	15.0	6.8
		24	14.0	4.2
		29	13.8	6.0
		33	19.4	6.8
		37	19.0	6.8
2	ii	19	12.4	6.0
		25		6.8
3	0	19	9.0	5.4
		27	10.0	5.0
		32		5.6
		37		5.0
		40	12.0	7.0
4	iv	13	13.0	5.0
		18	10.5	4.0
		22	10.0	4.0
		26		2.8
		30	14.2	3.6
		39	15.6	4.2
5	ii	21	8.0	4.0
		26	10.5	5.0
		30	11.4	4.8
		34	11.8	5.5
		38		6.5
6	ii	17	13.0	3.8
		21	10.6	3.0
		27	12.2	2.8
		32	13.8	3.5
		37	11.2	5.2
7	viii	28	13.2	5.6
		32	13.0	5.0
		36	15.0	4.0
8	iii	18	13.2	6.8
		22	13.4	6.8
		26	14.2	
		31	10.0	3.6
		35		5.4
9	0	18	9.0	3.0
		23	9.4	3.2
		27	13.6	3.6
		31	15.2	3.2
		35	15.6	6.8
10	0	17	10.8	3.4
		22		4.0
		27		4.8
		31	14.2	5.2
11	0	17	8.8	2.8
		24	9.0	3.0
		33	15.0	4.8
		37	11.8	4.8
12	0	19	10.6	2.4
		25	13.4	5.0
		29	15.8	5.0
		34	14.6	5.4
		38	14.6	4.8
13	0	21	13.4	
		27	10.6	3.4
		31	13.0	5.0
		36	15.8	4.2
		40	13.0	5.0

ponents being negligible factors. In other words, circulation time really measures the time required for the passage of blood through the lungs, and increase or decrease in time reflects a corresponding alteration in the speed of pulmonary circulation. Blumgart and Weiss<sup>23</sup> have shown that this time is independent of venous pressure, of vital capacity, of blood pressure, and only slightly affected by changes in the pulse rate.

Circulation time is related to cardiac output according to the formula which Stewart<sup>24</sup> derived in measuring blood flow through the lungs.

This formula is  $V = \frac{Q}{T}$  60, where  $V$  is volume output per minute in liters,  $Q$  is the quantity of blood in the lungs, and  $T$  is the mean pulmonary circulation time in seconds. It has been mentioned that the cardiac output increases progressively from the fourth month of gestation onward, which coincides with the increase in circulation time which we have found.

It is apparent from the equation that if  $V$  is to increase,  $Q$  must also increase or  $T$  diminish. That  $Q$  is increased can be deduced from the following facts. In the first place, with increased cardiac output, and slowing of the circulation as evidenced by progressive increase of arm-tongue time, it is obvious that there must be a greater amount of blood in the pulmonary capillaries. Second, there is a diminished vital capacity which is not sufficiently explicable on the basis of an elevation of the diaphragm. Alward<sup>25</sup> made vital capacity determinations before and after removing a huge ovarian cyst containing 15,000 c.c. of fluid and found no difference in vital capacity. Lemon and Moersch<sup>26</sup> have had similar results with ovarian cysts. That it is due to increased amount of blood in the lung capillaries, diminishing the alveolar spaces, is substantiated by the experimental studies of W. G. Harrison, Jr., Calhoun, Marsh, and T. R. Harrison.<sup>27</sup> They produced pulmonary congestion artificially and found vital capacity diminished correspondingly. On the other hand, rather than finding  $T$  diminished, we found it to increase progressively.

The great increase of circulation, through the viscera, particularly the uterus, causes a marked increase in the capillary bed. In a rigid tube system, the rate of flow is inversely proportional to the cross-section of the tube. This is not exactly applicable to the human system, which can undergo wide variations; but in view of the definite increase in capillary bed, the rate may be considered as diminishing according to the equation  $V = \frac{a}{\pi r^2}$ , where  $V$  is the rate of flow,  $a$  the volume of flow and  $r$  the radius of the tube corresponding to the cross-section of the capillary bed.

These physiologic changes of increased volume output, increased blood flow through the lungs and diminished vital capacity in pregnancy are present in hyperthyroid states. In hyperthyroidism there is a diminished vital capacity (Rabinowitch<sup>28</sup>), increased ventilation rate,

increased blood volume (Thompson<sup>29</sup>) and increased capillary bed from vasodilatation (Blumgart<sup>30</sup>). Anselmino and Hoffman<sup>31</sup> have attributed the changes in pregnancy to an increased secretion of the thyrotropic hormone of the anterior pituitary gland. There is very commonly in pregnancy a definite, palpable and visible increase in the size of the thyroid gland.

In spite of these similarities, there are several differences which should be pointed out. Most marked is the shortening of the circulation time in hyperthyroidism and the progressive increase of time in our series. The flushed moist warm skin in hyperthyroidism indicates the marked vasodilatation present. Despite the increase in cross-section of the vascular bed from vasodilatation, however, the circulation time is shortened and the rate of flow accelerated, showing the additional strain thrown on the heart by the abnormal stimulation.

In addition, we may point out that the progressive elevation of the basal metabolic rate in normal gestation, as noted by Plass and Yoakum,<sup>32</sup> is almost within normal limits, in contrast to the abnormally high basal metabolic rate in hyperthyroidism. Also, enlargement of the thyroid in pregnancy is due to increase in the colloid and not due to hyperplasia. Hyperthyroidism, therefore, cannot be used to explain the presence of dyspnea and easy fatigability in pregnancy.

Harrison<sup>33</sup> was able to produce dyspnea and diminished vital capacity by injecting blood into the pulmonary artery of dogs. He attributed the dyspnea to a vagal reflex excited by pulmonary congestion. This factor may also be responsible for the dyspnea in pregnancy. Krukenberg's<sup>34</sup> studies of blood lactic acid in pregnant women revealed a delay in the resynthesis of lactic acid to glycogen. Physiologists attribute fatigue to the accumulation of metabolites in the tissues, chiefly lactic acid, which are not adequately oxidized. According to Meyerhof's theory of oxidation, a portion of the lactic acid produced is completely oxidized, the energy produced being required to resynthesize the remaining lactic acid to glycogen. Insufficient oxygen hampers this resynthesis. Apparently, therefore, there is a failure in the respiratory function rather than in the circulatory. In addition, the relative anemia is responsible for less oxygen absorption in the lungs and therefore diminished oxygen transportation to the tissues.

#### CONCLUSION

1. By means of circulation time studies, it is possible to demonstrate a slight but progressive retardation of flow of blood in the course of pregnancy.

2. The symptoms and signs which simulate cardiac weakness in the course of pregnancy may be due to increased pulmonary congestion and may be of respiratory rather than cardiac origin.

We are indebted to Dr. Harry Aranow, Director of Obstetrics and Dr. Sol Biloan of the Department of Medicine, Morrisania City Hospital, for their encouragement and advice. We also wish to thank Miss Hildegard Boucher for her assistance.



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1147 HOE AVENUE

15 EAST CLARKE PLACE

## A NEW OPERATION FOR CYSTOCELE\*

G. D. ROYSTON, M.D., AND D. K. ROSE, M.D., ST. LOUIS, MO.

(From the Departments of Obstetrics and Gynecology and of Urology,  
Washington University School of Medicine)

THE repair of cystocele has frequently in the past given satisfactory results from a gynecologic viewpoint, only to leave considerable dysuria. Analyses of the types proving unsatisfactory were found to be those in which the urethra was severed from the trigonal muscle. This type of cystocele may be innocuous looking from the exterior, but its full extent is best appreciated on cystoscopic examination. It is our effort to recognize and repair this particular type, thus restoring the pelvic floor anatomically, and the bladder functionally, to a condition as nearly normal as possible.

The anatomy of the female bladder and urethra has received limited attention in textbooks, except in that of Kelly and Burnam, and efforts to review this phase of the subject have usually revealed relatively little of its physiology. Attention is directed to the importance of an intact supporting pubocervical fascia and the necessity of keeping the cervix uteri elevated to maintain normal position and relations.

The best information for the gynecologist on the anatomy and physiology of the female bladder was found in the work of Rex E. Van

\*Read before the St. Louis Gynecological Society, Dec. 10, 1936.

Duzen in his cystoscopic studies of cystoceles and his anatomic studies of the female trigone muscle, in collaboration with William W. Looney in the Department of Anatomy, Baylor School of Medicine, Dallas, Texas. These investigators give credit to Young and Wesson for their description of the male trigone and supplement this study with their work on the female trigone muscle.

This trigone muscle is a thin triangular sheet in the base of the bladder, bounded above by Mercier's bar, and below by the internal orifice of the urethra through which its fibers loop to fasten in the posterior wall of the urethra for a distance of approximately one-half the latter's length. The lateral margins of the trigone muscle are somewhat thickened and are called Bell's muscles. The trigone is covered with a smooth mucous membrane closely adherent to the underlying muscle coat, thus forming a smooth, firm platform, even when the remainder of the empty bladder is in folds.

In women with normal bladders, the ureteral orifices are about 3 cm. apart and 3 cm. above and behind the internal sphincter, the urethra being approximately one to one and one-half inches long. Bladder injury may make this distance vary with the location and extent of the injury, the tendency being to make the distance greater in injury below Mercier's bar, whereas damage above Mercier's bar shortens this distance. In some cases, the cystocele may involve tissues both above and below Mercier's bar.

In the female, Van Duzen and Looney find that the internal sphincter consists of "two portions, namely inner and outer," and "the most internal fibers form a complete sphincter around the internal orifice of the urethra," while "the outer portion of the inner bundle appears to loop partially around the urethral orifice. The outer portion of the sphincter lies external to and somewhat below the inner portion;" the fibers begin on the posterior wall and pass on each side of the urethral orifice to its anterior surface. The external portion extends down the urethra to the urogenital diaphragm. Thus we have a loop muscle arrangement extending from the internal sphincter bladder surface to the urogenital diaphragm, and it is through this aperture that the trigonal muscle passes to be attached in the urethra. Young showed that the internal sphincter is opened by the downpull of the trigonal muscle, passing in the form of a bow through the weaker arcuate muscles, comprising the internal sphincter, at the vesical orifice (see Fig. 7). When the trigonal muscle is torn near the point at which it passes through the internal sphincter, this latter circular muscle is released from the effects of the downward pull occasioned by voiding, and in consequence of this release, internal sphincter spasm occurs. Long duration of this spasm invites mucosal hyperplasia on the contacting surfaces of this released internal sphincter. A vicious circle is now established in that the hyperplastic urethral tabs irritate the

sphincter to greater contraction. It is this sequence of events that particularly may account for bladder irritability, even in the absence of a cystitis. Such an injury to the trigone muscle causes a delay in starting the stream and necessitates straining, because the sphincter must now be opened by increased intravesical pressure rather than by the trigonal muscle.

The majority of cystoceles observed are damaged near the point of fascial attachment between the cervix and bladder, that is, above Mercier's bar, where any standard plastic repair that elevates the cervix and supports the bladder floor will effect a cure. However, there is a relatively small percentage of cases in which the trigone muscle is damaged or sheared off from the internal sphincter, the injury being below Mercier's bar, and permanent cures are relatively rare. It is for this particular type of cystocele that we now suggest this method of anatomic repair and restoration of physiologic func-

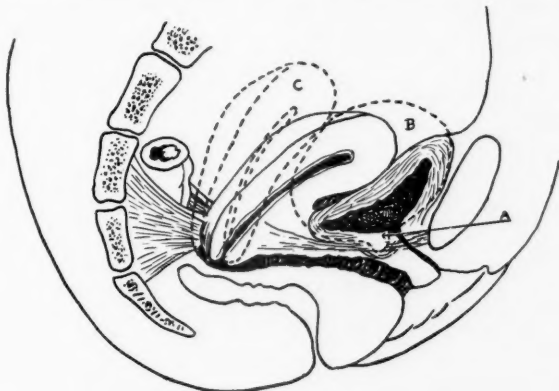


Fig. 1.—Uteropubic fascia and uterosacral ligaments. Schematic drawing of this particular type of cystocele (A) when bladder is distended (B) displacing corpus uteri (C). (From Farrar in Curtis' *Obstetrics and Gynecology*.)

tion, which consists in functionally reuniting the severed, or partially severed, portions of the trigone muscle above the internal sphincter with that small portion which is anterior to the internal sphincter and which serves as its attachment in the urethra. In the main, this is done by first drawing these two portions together near the internal sphincter with sutures parallel to the long axis of the urethra, and then supplementing this functional repair by splinting these two portions with tissue from beneath the anterior urethra to the posterior area of the trigone. This fascial splinting is carried to the uterine body as in the standard advancement operations described in textbooks by Crossen, Curtis, and Graves. The following prophylactic measures are suggested to lessen the tendency of trauma producing cystocele:

1. Proper management of labor to insure a normal mechanism, avoid too rapid deliveries and injudicious instrumental applications, resort more frequently to episiotomy.

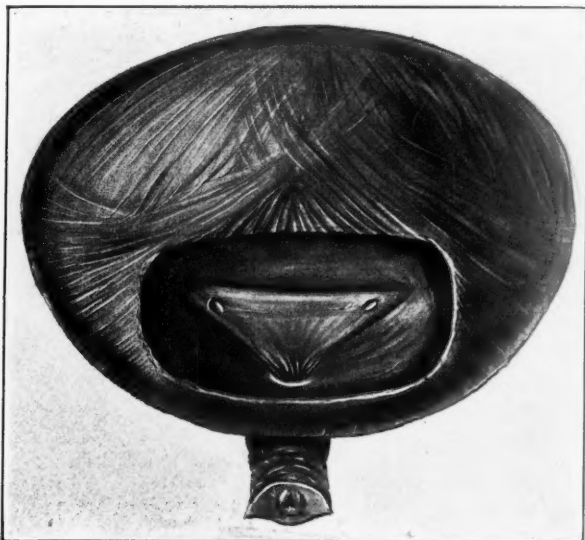


Fig. 2.—Anterior view of distended bladder exposing trigone and base of bladder. (From Kelly and Burnam.)



Fig. 3.—Diagrammatic representation of normal curve of urethra, trigone, and bladder floor. (Modified after Kelly and Burnam.)

2. In cases of partial injury to the trigonal muscle, with release and consequent spasm of the internal sphincter, urethral dilatation to the point of tolerance is advisable during the early puerperium.

Routine cystoscopic examination, prior to all cystocele repair operations, is advised as a diagnostic aid in order to determine the location and extent of the injury. With the bladder filling slowly and not too full, have the patient strain, and through the cystoscope note:

1. Whether the sphincter depresses promptly and directly with the contractions of the trigone muscle when the patient tries to void.
2. If any cystocele is present, and if it is above or below Mercier's bar.
3. The presence and location of any true or pseudodiverticula.
4. The presence of trabeculae (hypertrophied muscle in the bladder wall) in early cases, and the thin, atrophic bladders in those of long standing.
5. The presence or absence of a relaxed or spastic internal sphincter.



Fig. 4.—Diagrammatic representation of point of injury anterior to Mercier's bar where the urethra is sheared from the trigonal muscle near the internal sphincter. Note abnormal curve of urethra, due to elevation of the internal sphincter. (Modified after Kelly and Burnam.)

6. At the height of a bladder contraction, note the distance from the internal sphincter to the floor of the trigone.

7. The presence or absence of any contracting torn ends of the trigonal muscle.

The damaged internal sphincter is a prime cause of urinary incontinence. If the cystocele is anterior to Mercier's bar, the result will depend upon the ability of the remaining trigone muscle fibers to compensate and perform the function intended for the whole; hence, when such injury is present, early repair, before loss of bladder tone, offers the best hope of cure.

In many instances of the particular type under discussion, there will be very little external evidence of cystocele. However, on cystoscopic examination, with the patient straining, the urethra, being sheared



off the internal sphincter, does not depress with the trigone. In other words, when the patient strains, there may be even a definite urethral obstruction, first, in spasm of the internal sphincter, and second, in that the latter is relatively raised from the floor of the bladder. It is to correct this last defect in particular, that this operation is devised. As the operation probably does not actually unite the severed ends of the trigone muscle, but approximates them enough to function, some individuals may occasionally require subjective relief by urethral dilatation after operation. Such dilatation would be the exception

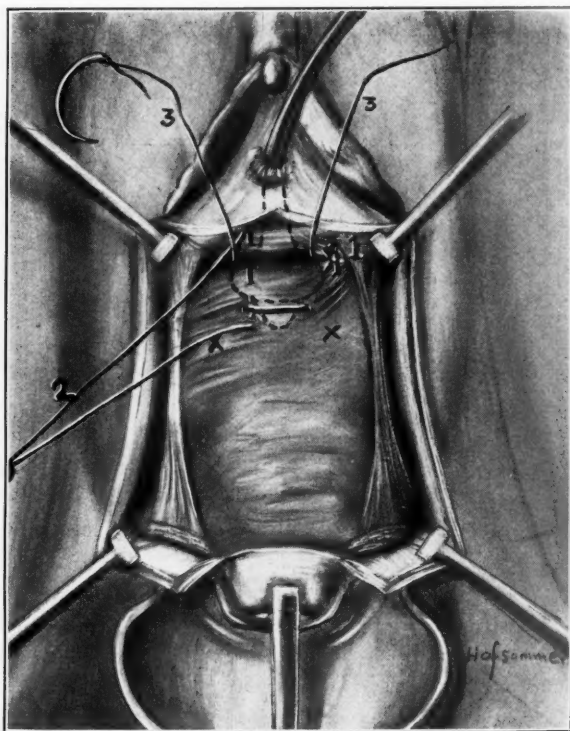


Fig. 5.—Traction on mushroom catheter marks site of internal sphincter just anterior to bulbous tip. X marks the location of the ureteral orifices. 1, Anteroposterior suture tied. 2, Similar suture on opposite side placed from a point three-fourths of an inch anterior to and carried to a point three-fourths of an inch posterior to the internal sphincter. 3, Mattress suture placed for reinforcement at the internal sphincter. Catheter is removed before any sutures are tied.

and it might well, in a few instances, be supplemented by cystoscopic diathermy of any urethral tabs which could initiate the spasm and thus cause symptoms.

This type of injury is very frequently associated with urethrocele due to internal sphincter damage, but is a distinct clinical entity.

#### OPERATION

Under morphine-hyoscine and local infiltration with one-fourth of 1 per cent of novocaine to which is added four minims of 1-1,000 adrenalin per ounce, an inverted

T-incision is made through the anterior vaginal wall from the cervix to a point within 1 cm. of the meatus. A large volume of infiltrating fluid facilitates dissection of the vaginal flap from the bladder. The nearer one approaches the meatus; the more difficult is the dissection. Great care must be taken to avoid injury to the urethra. The bladder is freed from the uterus by blunt dissection almost as high as its peritoneal reflexion. The incision near the cervical tip is carried bilaterally far enough to expose the bases of the broad ligaments. A number eighteen French, mushroom tip catheter is inserted into the bladder, and traction on the catheter marks the site of the internal sphincter, just in front of the bulbous tip, making due allowance for any marked urethrocele. A fine catgut suture, preferably 00 or 000 chromic, on a fine curved intestinal needle, takes a deep bite anteroposteriorly

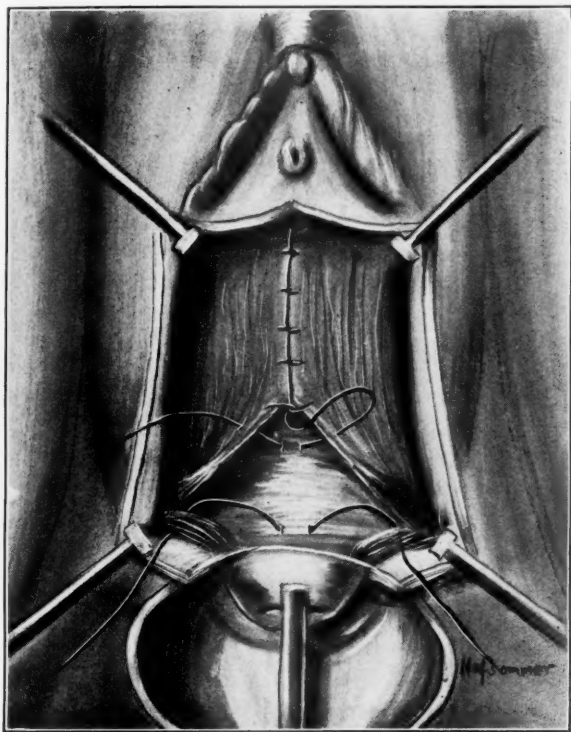


Fig. 6.—Plication of fascia with fine chromic catgut beginning as near the meatus as dissection has made visible and carried posteriorly to the corpus uteri to which it is fixed, advancing the bladder to a higher level. Bases of broad ligaments are sutured in front of the cervix which is elevated.

in the tissue close to the side of the urethra, three-fourths of an inch or more, in front of the internal sphincter, and is carried in the vaginal axis, intermittently, through the outer thickness of the bladder wall posteriorly to a point three-fourths of an inch behind the internal sphincter, not crossing the midline of the body. Emphasis is placed on carrying the suture anteriorly to a point within 1 cm. of the meatus. The suture should not be carried high enough posteriorly to obstruct the ureter, which is normally 3 cm. behind the internal sphincter. The two ends of this suture are not tied until a similar suture is placed on the opposite side of the urethra, thus fixing both sides of the trigone muscle to the urethra anteriorly to the internal sphincter. When the cystocele is marked, a third such suture may be placed in the midline, from beneath the urethral wall to a point well back on the

base of the trigone muscle. These sutures restore the normal axis of the urethra. A deep mattress suture then reinforces the internal sphincter and fixes it to the trigonal muscle. The mushroom catheter is removed before any sutures are tied. A running lock-stitch of fine chromic catgut then plicates the fascia from a point near the meatus all the way back to the corpus uteri to which the fascia is elevated and fixed as high as possible. A second running lock-stitch (or half lock-stitch), using No. 1 chromic catgut, then reinforces this fascial attachment, avoiding undue tension. The bases of the broad ligaments are sutured anterior to the cervix to elevate same, and the vaginal wall is approximated with a continuous lock-stitch of No. 1 chromic catgut, after excising any redundant tissue, taking care to leave ample flaps for approximation. In cases of vaginal hysterectomy, the cardinal supporting ligaments of the uterus are plicated beneath the bladder in the customary manner. A perineorrhaphy is usually done after completion of the anterior colporrhaphy. This repair elevates the cervix, bladder floor, and urethra. It enables the patient to empty her bladder without undue strain. It is an attempt to restore anatomic relations of the trigone so as to permit satisfactory function. Thus far, we have done six operations by this method, five of which have functioned satisfactorily. The sixth patient was improved; though failure to carry the repair suf-

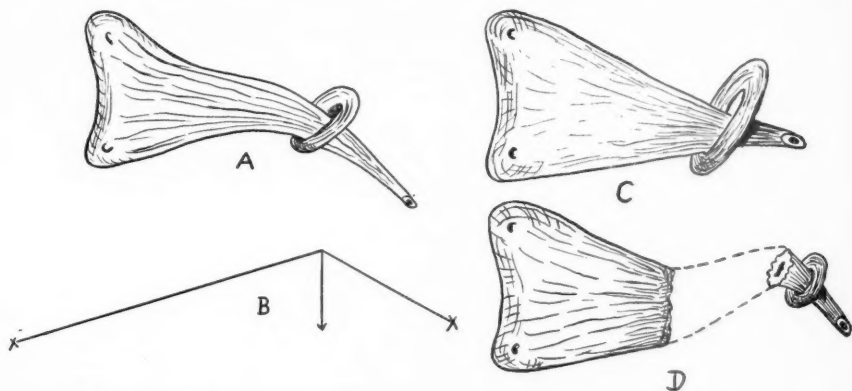


Fig. 7.—Schematic modification after Van Duzen, from Young's *Urology*. A shows the normal trigonal muscle passing through internal sphincter. It is fastened in the floor of the urethra. B shows angle of traction during voiding. C shows trigonal muscle, thicker and shorter in contraction, opening the internal sphincter. D shows trigonal muscle severed at or near internal sphincter.

ficiently far anteriorly to the internal sphincter did not give complete relief from urinary frequency, because of imperfectly fixing the urethra to the trigone. It is suggested as a method of repair in cases where satisfactory results have not been obtained up to the present time.

#### SUMMARY

This operation is devised for the specific type of cystocele described, where methods of repair thus far have been unsatisfactory. This correction lies in splinting the entire urethra, excepting the anterior 1 cm., by means of a running catgut stitch, which continues past and through the lower segment of the internal orifice to a point posterior to the midtrigonal region.

This suture, besides uniting and splinting the urethra to the trigone, pulls down the anterior urethra and meatus and fixes the internal

orifice to the line of suture. In addition to the splinting suture described, are those sutures placed parallel to the long axis of the urethra which, besides supplementing the effects of the running urethral trigonal lock-stitch, also bunch tissues at the internal orifice. This latter bunching effect in turn is supplemented by a mattress suture overlapping the fascia.

This functional bladder repair may be incorporated, in suitable cases, in any standard operation for repair of cystocele.

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### THE EARLY DIAGNOSIS OF ABRUPTIO PLACENTAE AND ITS TREATMENT WITH WHEAT GERM OIL

EVAN SHUTE, B.A., M.B., F.R.C.S.C., LONDON, ONTARIO

(From the Department of Obstetrics and Gynaecology, University of  
Western Ontario)

**A**BRUPTIO placenta under one or other of its numerous names has been a well-recognized entity for many years. It has been variously referred to as accidental hemorrhage, concealed hemorrhage, ablatio placenta, and premature separation of the placenta. The lesion thus referred to is really a premature, and usually partial, separation of the placenta which lies on the fundus or sides of the uterus but not in the position we describe as previa.

#### INCIDENCE

The incidence of this condition is variously given by the different clinics and authorities. It ranges from 0.18 per cent (Kraul) to 1.06 per cent (Cragin, Goethals<sup>1</sup>), or even 2.8 per cent (Baird<sup>2</sup>). Either there is a very great variation in its incidence in various parts of the world, or there is a variation of opinion as to what should be classified in this pathologic group. We believe the latter is the more likely explanation. Undoubtedly many cases of this type are overlooked, both in hospital and home practice, because placentas are not examined routinely and minutely by competent obstetric pathologists. Moreover there is lacking in the literature an adequate description of the signs and symptoms which characterize early or mild degrees of abruptio placenta. As a result, only the most startling and striking cases are ever recognized as such.

## SIGNS AND SYMPTOMS

The classical textbook description of these cases mentions that there is usually a background of toxemia; that the lesion develops in the last trimester of pregnancy, and is characterized by the sudden onset of a small amount of bleeding out of all proportion to the accompanying constitutional signs of shock. Indeed there may be no bleeding evident at any time, hence the appellation, concealed hemorrhage. With or without bleeding, there is the sudden development of uterine pain and tenderness, accompanied by uterine rigidity of such a nature as to give a woody or doughy feeling on palpation. There may be even some generalized abdominal rigidity and tenderness if the lesion is sufficiently gross. There are increased or agonal fetal movements, which end in the death of the fetus if the placenta separates sufficiently, or separates near the cord insertion. In any case there is usually evidence of some sort of dire fetal distress. The outstanding aspect of the picture, perhaps, is the generalized shock. As it resembles surgical shock from other causes, there is no need to enumerate its details here.

The termination of such a case may vary. Either the hemorrhage is profuse and intractable and the woman dies, or the hemorrhage may be scarcely revealed but be extensive internally and have the same termination; or the placenta may separate completely, the fetus die, the lesion become quiescent, and a "missed abortion" be carried for a time until labor sets in and the macerated fetus and placenta are expelled. On the other hand the lesion may be small, only a little of the placenta may separate; then for some reason the whole process subsides, may or may not recur, and the pregnancy goes to term or to near term, a live baby is delivered, and the placenta displays one or more large or small marginal infarcts or organized clots.

We do not feel, however, that the true picture of all cases of abruptio placentae is adequately represented by the foregoing description. In a previous paper<sup>3</sup> it was pointed out that just as a pregnant woman showing polyneuritis and icterus after prolonged hyperemesis can scarcely be said to represent completely the classical evidences of hyperemesis gravidarum, in the same way such severe cases as the texts describe do not represent the entire group of cases which should be labeled abruptio placentae. Myxedema is not the typical and exclusive picture of hypothyroidism. Until we come to a more typical and accurate clinical description of abruptio, we shall fail to recognize early cases and be unable to administer prophylactic therapy. We will be forced to fall back upon the pessimistic view expressed recently by Baird in his review of ten years' experience at the Glasgow Maternity. He concluded "antenatal care can do little in the prevention of accidental hemorrhage."

In the course of a detailed study of the problem of the premature interruption of pregnancy, the details of which have been published else-



where,<sup>4-7</sup> we came across a group of cases which we wish to present for consideration in this regard. At any time these cases might terminate in a typical abruptio with the classical signs and symptoms described above. We found these cases very numerous, indeed, and wondered if abruptio placentae could really be as frequent in a mild form as this would indicate. At about that time we came upon the study of Goodall,<sup>8</sup> who in 750 placentas obtained from consecutive deliveries in Montreal, found that 600 bore evidence of some hemorrhagic lesion but that in only eleven instances had there been bleeding from the vagina during gestation.

The most frequently encountered and significant sign in these cases, by all odds, was the gradual appearance of a restricted, palm-sized area of true uterine tenderness, accompanied by steady sacral backache. Occasionally these features were soon followed by the occurrence of labor pains, violent fetal movements, and uterine hemorrhage of any grade of severity. Or a gradual elevation of blood pressure developed, accompanied by edema of the extremities, rapid gain of body weight and even albuminuria, indicating an early toxemia or pregnancy. The uterine tenderness in severe cases usually spread over the whole uterus or a large area of it. It might, however, disappear spontaneously, together with all the other signs or symptoms mentioned except the evidences of toxemia. If the latter once showed themselves they tended to persist and progress as is usual. When the same signs and symptoms of tenderness, pains, and hemorrhage recurred, as often happened, the area of tenderness was in the same location as before. In four instances we were able to determine that this area of tenderness coincided accurately with the placental site. These were cases of manual removal of the placenta at cesarean section or at the extraction of twins per vaginam.

When these women went on to miscarry or deliver at term, with or without treatment, the placentas were usually small for the duration of the gestation. Almost always they displayed one or several marginal lesions, ranging in character from fresh blood clot to recently organized, leached clots resembling cheese in consistency—or even appearing as white infarcts. These white infarcts might be 2 or 3 mm. deep on the maternal aspect of the placenta or might penetrate through the placental substance to the fetal side. The frequency of such placental lesions was quite comparable to that mentioned by Goodall. Women who expelled such damaged placentas could usually recall one or more slight or severe hemorrhages during gestation or perhaps a transient but definitely localized area of tenderness on the uterine wall. When this had disappeared and recurred, it had always recurred in the same location. However, placentas might be grossly normal in classical cases of abruptio placentae where there could be no doubt as to the clinical diagnosis. The reverse was also true, viz., that a placenta with

undoubted evidences of much recent organized blood clot at its margin might be expelled by a woman who could not remember anything one might link up with such a diagnosis.

We observed cases of the type we have described more frequently in the late winter and spring than at any other time of year. They were least frequently encountered in the late summer and early autumn.

#### SEROLOGIC STUDIES

As was mentioned, we were engaged in a study of all types of cases of premature interruption of pregnancy, and this group of cases bulked large in such a series. It occurred to us, therefore, to test their blood serums for evidence of the imbalance between vitamin E and estrogenic substance which characterizes most women who are aborting or miscarrying spontaneously. We have developed a simple laboratory test<sup>4</sup> in order to disclose vitamin E deficiency or excess of estrogenic substance in the blood and, accordingly, this was employed. We might add that certain uncompleted spectrophotometric studies of these serums, which we have carried out under the direction of Mr. G. A. Adams of the Department of Biochemistry, gave us no reason to think that vitamin C deficiency was present. Moreover, we have seen classical cases of abruptio develop in women whose C intake was unusually high.

Our results are tabulated here. In the first year of our investigation we paid very little attention to the cases of abruptio. As our interest was aroused, however, and a more sensitive test for E-deficiency was developed, we secured very interesting results. Evidences of vitamin E deficiency seemed to be intimately associated with the clinical signs and symptoms we have described. We excluded seven cases from consideration in which the test was done long after the placental detachment had been responsible for fetal death, because our test is useless very soon after complete placental detachment, whether normal or abnormal, has occurred.

DURATION OF EXPERIMENT	NUMBER OF CASES	PERCENTAGE SHOWING A RELATIVE DEFICIENCY OF VITAMIN E AND THEREFORE AN EXCESS OF BLOOD ESTROGENIC SUBSTANCE
Jan. 1, 1934—Jan. 31, 1935	5 cases	80 per cent
Feb. 1, 1935—May 31, 1936	77 cases	78 per cent
29 months in all	82 cases	78 per cent

Of these 82 cases, only 31 were of the severe classical type described in standard works. Of these 31 severe cases, 81 per cent revealed vitamin E deficiency.

#### WHEAT GERM OIL THERAPY

In a series of 44 cases of spontaneous abortion we had found that 73 per cent showed evidences in the blood serum of deficiency of vitamin E.<sup>4, 6</sup> It has now become generally recognized<sup>9-11</sup> that vitamin E has great prophylactic and therapeutic value in the treatment of abortion.

It is quite understandable, therefore, that we began to study the corresponding use of a vitamin E preparation with which we were thoroughly familiar\* in cases of abruptio placentae. Such an oil must be kept cold, and be not more than eight weeks old.

The results have been very encouraging, although it is too early yet to assess them properly. Obviously those patients first seen when placental detachment is already complete or nearly complete offer little excuse for anything but the classical measures used everywhere for such an emergency. We cannot but suspect, however, that a closer search for true uterine tenderness during pregnancy, combined with an early test of the blood serum for the presence of the specific hormone-vitamin imbalance we have described, would to a great degree prevent the occurrence of such severe cases.

It has been our experience with the less severe cases that, when properly and adequately saturated and kept saturated with vitamin E (as determined by clinical evidence and repeated tests of the serums), they have not progressed to a severe stage of placental detachment with death of the fetus. In approximately twenty hours, an adequate massive dose of eight to twelve drams of bulk wheat germ oil has completely abolished the characteristic circumscribed area of uterine tenderness. The accompanying severe sacral backache and uterine cramps have subsided as rapidly. When uterine hemorrhage has been present, it has responded promptly as well. Within the first day of treatment the patients have remarked that their indescribable subjective discomfort has disappeared. One patient who developed a Couvelaire apoplexy of the uterus described these sensations as resembling those of "a cold coming on." Stopping the oil therapy has often been followed by a recurrence of uterine tenderness and bleeding, which, in turn, have disappeared on further vitamin E therapy. No case recognized early and treated adequately has gone on to the severe classical type.

Our best results have been obtained in women who showed little or no evidence of an associated toxemia. We can say in passing, however, that where such toxemia was detected very early, at the first rise of blood pressure beyond the accepted critical level, at the first continued excessive gain of weight or appearance of edema, at the first mild albuminuria or in patients in whom by abdominal palpation the fetus seemed unusually small in consideration of the duration of gestation or was surrounded by some excess of amniotic fluid, wheat germ oil therapy was immediately beneficial. The blood pressures, both systolic and diastolic be it noted, returned to normal levels and were maintained there as long as the patient remained saturated with wheat germ oil. Albuminuria ceased. The unusual rate of weight gain was diminished, or the patient might even lose weight. Edema decreased, sometimes with frequency and polyuria, and all this without the use

\*Viteol, supplied by the Canada Pharmacal Company, London, Ontario.

of salt-restriction, bed rest, or other standard measures. Some of these small fetuses seemed suddenly to increase in size in an amazing way. As we are well aware of the fallacy of estimating fetal size by abdominal palpation, we have recently begun to check this observation by more accurate roentgenologic means.

However, in women in whom the evidences of toxemia were of some duration, the beneficial results of the wheat germ oil therapy, at least as far as it concerned the signs of toxemia, were scarcely discernible. But such of these cases as displayed deficiency of vitamin E (or excess of estrogenic substance) in the blood serum did not go on to true eclampsia, in our limited experience, and with adequate vitamin E therapy could be safely induced when gestation was sufficiently advanced. The placentas adhered sufficiently well to enable induction and labor to proceed safely for mother and child.

#### DISCUSSION

Years ago Holmes<sup>12</sup> foreshadowed the division of the toxemias of late pregnancy into those which went on to eclampsia and those ending as *ablatio placentae*, as he called the lesion under discussion. There seems to be considerable justification for such a point of view. We see very few true eclampsia cases in this locality, but there have been eight such cases in the past three years whose blood serum we have tested for vitamin E deficiency and excess of estrogenic substance. Only one of the eight showed the defect in the particular hormone-vitamin balance just mentioned. Similarly Bickenbach and Fromme<sup>13</sup> found no increase in the blood folliculin content in four eclamptic patients they observed. Indeed it would appear from the work of the Smiths<sup>14</sup> that the blood and placentas of eclamptic patients are characterized by a low estrin and an excess of the antagonistic anterior pituitary gonadotropic hormone. Indeed, we have recently treated a convulsive eclamptic patient and a severe late preeclamptic patient by means of estrin with very suggestive and beneficial results.

Holmes,<sup>12</sup> Baird,<sup>2</sup> Davis and McGee,<sup>1</sup> and others have pointed out that abruptio placentae is only rarely associated with eclampsia or eclampsism. Le Lorier,<sup>15</sup> for example, in 31 cases of hematomas retroplacentaires found only two associated with eclampsia. We suspect that the late toxemias of pregnancy may prove to be divisible into two main groups, those deficient in vitamin E and displaying an excess of estrogenic substance in the blood, and a very much smaller group with adequate vitamin E and characterized by an excessive excretion of prolactin. The former are cases in which abruptio placentae is actual or impending, the latter are cases in which true eclampsia is actual or impending. We have observed that those cases in which the excess of estrogenic substance was most marked were generally hypothyroid, and perhaps that feature of the endocrine picture of the toxemias should also receive notice. Hoffmann and Anselmino<sup>16</sup> found that there was a great decrease of thyroid secretion below the normal for pregnancy in the blood of pregnant women showing renal damage, but that in eclampsia the content of thyroid secretion was much higher than the values for normal pregnancy.

In previous papers<sup>5, 6</sup> we have expressed the belief that vitamin E in the pregnant woman acts by neutralizing estrogenic substance which, when present in excess, resists the intrusion of the placental villi into the uterine wall. We endeavored to explain in this way the fundamental mechanism of abortion, miscarriage, and premature labor. Perhaps the mechanism underlying the development of abruptio placentae is not dissimilar.

McGlinn and Harer<sup>17</sup> have recently expressed this possibility in very thought-provoking words, "All writers stress traumatism, endometritis, diseases of the ovum, emotional states and toxæmia. It is quite possible that we must look to the early development of the placenta for the real underlying cause. This embryologic factor may quite possibly be a paucity of anchoring villi, so that the placenta is from the very beginning only loosely attached to the decidua basalis. Such a placenta, particularly when subjected to the additional pathologic changes that so frequently accompany late gestational toxæmia, would naturally be expected to separate from its uterine attachment—unquestionably, a placenta that is the site of large infarcts is less firmly attached to the decidua than is a normal noninfarcted placenta."

Many interesting avenues for further investigation are opened up by this study. It offers a further aid in the differentiation of abruptio placentae and placenta previa. Theobald<sup>19</sup> has expressed the belief that all the toxemias of pregnancy may prove to be interrelated and due to dietetic deficiencies. This may be as true for the group of abruptio cases as for the neuritis cases with which he has been engaged.

New insight into the problem of nephritis, as associated with pregnancy at least, and all its related pathologic phenomena may also develop from it. Interesting possibilities of antagonisms and synergisms existing between the hormones and vitamins present themselves. With such antagonisms as exist between estrin and progestin or estrin and anterior pituitary gonadotropic hormone, or such synergism as that existing between estrin and postpituitary oxytocic hormone, we are already familiar. Collip<sup>19</sup> and others have suggested the presence of anti-hormones for hormones other than estrin.<sup>20</sup> It is known that vitamin D is estrogenic. But this picture of an equilibrium existing between estrogenic substance and vitamin E is not quite identical with any such relationship as has been mentioned.

#### SUMMARY

1. Many cases of abruptio placentae are overlooked because the early symptoms are not recognized.
2. The early symptoms are described in detail, stressing localized uterine tenderness and sacral backache.
3. The marginal retroplacental hemorrhages and clots are described briefly.
4. Seventy-eight per cent of 82 cases of mild and severe abruptio placentae showed serologic evidences of deficiency of vitamin E.



5. Wheat germ oil, therefore, was used prophylactically and therapeutically. The results were very satisfactory.

6. The relationship of this new evidence to the problem of the toxemias of late pregnancy is discussed.

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## CYSTOGRAPHIC DIAGNOSIS OF PLACENTA PRÆVIA

JAMES F. McDOWELL, M.D., BIRMINGHAM, ALA.

(From the Department of Obstetrics, Hillman Hospital)

PLACENTA previa is associated with such a high mortality, both fetal and maternal, that even a suspicion of the condition leads to grave apprehension on the part of the attending obstetrician and often to too rapid a decision for cesarean section. Since the advent of the x-ray there have been innumerable attempts to use this procedure as an aid in the diagnosis.

Campbell and others in 1932 mentioned the possible use of strontium iodide as a means of diagnosing the position of the placenta in utero. Menees, Miller, and Holly in 1930 injected strontium iodide into the uterine cavity through the abdominal and uterine walls, thus making the amniotic fluid opaque to the roentgen rays. By this method the placenta could be outlined as a bulging mass or a filling defect into the cavity. They noted that in many of the cases labor was instigated and that premature delivery was the result. Snow and Powell<sup>1</sup> in 1934 report that Snow first recognized the placenta in a simple flat plate of the abdomen. They were able to demonstrate the position of the placenta and explained that the placenta causes an obstruction to the rays due to the greater density of the tissues and blood vessels that made up the placenta in contrast to the lesser consistency of the amniotic fluid. They also suggested the possibility of using this method as a possible means of diagnosing placenta previa. Ude, Weum and Urner<sup>2</sup> also in 1934 reported the positive diagnosis of three cases of placenta previa and one of premature separation of the placenta by the use of sodium iodide injected into the bladder followed by a cystogram. The placenta was demonstrated as a mass be-

tween the fetal head and the upper concave border of the bladder. They made the note that the procedure was not satisfactory in cases of breech or transverse presentation. In 1935 Ude and Urner<sup>3</sup> studied all cases of abnormal bleeding that came to their attention and reported fourteen positive cases of placenta previa as diagnosed by the cystographic method. All of their cases were confirmed at operation with the exception of one in which there was no note made as to the position of the placenta. They also made a study of normal cases on which to base their diagnosis of abnormal position of the placenta. They found that in the full-term pregnant woman there is a distance of approximately 1 cm. between the upper concavity of the bladder and the lower convexity of the fetal head as it descends into the pelvic canal (Fig. 2). The demonstration of a mass between the head and the bladder constituted their diagnosis of either a previa or a blood clot when the clinical manifestations were suggestive of some pathology.

The scope of this paper is to present nine cases of abnormal uterine bleeding during the last trimester of pregnancy in which the diagnosis of placenta previa was made in seven as a result of cystographic examination. In the seven cases cesarean section was elected as the method of delivery of choice.

#### TECHNIC OF THE CYSTOGRAM

A cystogram was done on all patients who were admitted with a history of abnormal bleeding during the latter months of pregnancy, or who came to the hospital not necessarily in labor but because of bleeding. The patient was first catheterized to empty the bladder completely. We then used the technic as outlined by Ude and Urner with few minor variations. From 30 to 40 c.c. of an opaque material, usually 12½ percent sodium iodide, was then injected into the bladder and the catheter removed. A flat plate of the lower abdomen with the patient in the supine position was then made. An effort was made to prevent a tilting of either the table or the tube thus permitting the rays to pass straight downward. The first plate was then immediately developed and read. If there was too much material in the bladder, as evidenced by an "overlapping" of the upper border, from 10 to 15 c.c. was removed and a second plate made. A large enough film was used to permit exposure of the entire pelvis and approximately half of the fetus.

#### CRITERION OF DIAGNOSIS

As noted by Ude and Urner there is normally a distance of about 1 cm. between the fetal head and the upper margin of the bladder. This distance should be the same across the entire top of the bladder. In the majority of our cases where a positive diagnosis of previa was made there was usually on one side the expected 1 cm. (more or less) with a gradual or sudden widening out as the opposite side was approached, until a distance of sometimes 3 or 4 cm. was obtained (Figs. 1 and 3). We considered this as suggestive of marginal placenta previa. A separation of from 2 to even 4 cm. across the entire upper margin of the

bladder and an associated suspicious history led us to consider the patient to have a complete or central placenta previa (Fig. 4). It must be borne in mind that the presence of blood clots from a premature separation, which have settled into the lower uterine cavity, is capable of giving a similar picture, either of the marginal or central type. In either event the condition would in all probability be abnormal. In all doubtful cases the plates were either repeated or the patient observed until she showed more definite signs of the condition.

In our cases we observed that the cystogram was satisfactory only during the last trimester of the pregnancy, due to the fact that in earlier pregnancies the head was still floating above the brim of the pelvis with the result that there was no pressure being made on the bladder. It is better to have the patient in the early first stage of labor or at least have the head below the brim. In the presence of prematurity the fetal head is not large enough to entirely fill the pelvis, with resulting unsatisfactory pictures. The entire diagnosis depends upon the ability of the fetal head to exert pressure downward onto the bladder. The amniotic fluid, acting as a transmitting agent, will then give the desired pressure on the urinary bladder, causing the even concavity of its upper border.

#### CASE REPORTS

CASE 1.—Mrs. M. B., aged twenty-one, para 0, gravida i, was first seen in the prenatal clinic on Mar. 25, 1935. Last menstrual period was in November, 1934. Physical examination at the first clinic visit was essentially negative. Pelvic measurements adequate. Prenatal period uneventful except for "hematuria" on Apr. 29, 1935. Patient was admitted to the hospital on July 19 with a history of having painless vaginal bleeding on July 18, similar to normal menstruation. Membranes were intact on admission. Some complaint of aching low in the back and right side. Physical examination negative. The abdomen was the size of a full-term pregnancy, head not engaged, and the fetal heart tones well heard in the left lower quadrant. On the day after admission the bleeding had checked but there was still some cramplike pain in the abdomen. She had no more bleeding or pain and on July 24 a cystogram was done with a diagnosis of probable placenta previa (Fig. 1). Laparotrachelotomy was done on July 26 and a living child delivered, which died about six and one-half hours after delivery. (Autopsy on the baby revealed bilateral congenital atelectasis.) The placenta was found to be laterally placed. Convalescence of the mother was uneventful and she was discharged on August 4.

CASE 2.—Mrs. R. L., aged twenty-six, para i, gravida ii, admitted to the hospital on July 24, 1935, with a history of rupture of the membranes on July 19 and the onset of uterine bleeding on July 23. General physical examination was essentially negative. The fundus uteri extended to two fingers above the umbilicus with the fetal heart tones heard in the left lower quadrant. A cystogram was done soon after admission but was unsatisfactory due to the prematurity of the fetus. She was observed for three days, went into labor on July 27 and delivered a living premature child that day. The placenta was normally placed. Puerperium uneventful.

CASE 3.—P. T., aged forty, para vi, gravida vii. Last menstrual period was Dec. 5, 1934. First seen in the prenatal clinic on June 12, 1935. Physical examination at that time was negative. Pelvic measurements adequate. Admitted to the hospital on August 10 with a history of profuse painless bleeding early that morning. Membranes intact. General physical examination was negative. Fundus was about the size of a full-term pregnancy, with the fetal heart tones well heard in the left lower quadrant. Position left occiput anterior. Cystogram done on August 10 and a diagnosis of partial or central placenta previa made. Cesarean section



Fig. 1.—Mrs. M. B., aged twenty-one, para 0, gravida i. Cystographic findings similar to those in Fig. 2 but which are not as well defined. There is a gradual increase in the separation beginning about 3 cm. from the left border of the bladder toward the right. A positive diagnosis of right lateral placenta previa was made



Fig. 2.—Mrs. A. P., aged twenty, para 0, gravida i, admitted with history of painless uterine bleeding. Cystographic findings illustrated that there was a constant distance between the fetal head and the upper concavity of the urinary bladder. At delivery the placenta was found to be normally placed.

done on August 10 and a living child obtained. The placenta was partially occluding the internal os. Convalescence of the mother was very satisfactory until the ninth postoperative day when she began complaining of pain in the left chest. She subsequently developed an abscess in the left upper lobe of the lung which was drained by the two stage thoracoplasty method. Discharged from the hospital as healed on Nov. 19, 1935.

CASE 4.—Mrs. A. P., aged twenty, para 0, gravida i, clinic patient with an uneventful prenatal period until Sept. 14, 1935, when she began having a slight amount of painless uterine bleeding. Admitted to the hospital on September 16. Membranes intact. Physical examination negative. Fundus three fingers above the umbilicus with the fetal head at the pelvic brim. Fetal heart tones in the left lower quadrant. Position left occiput anterior. Cystogram done soon after admission which was negative for previa (Fig. 2). Bleeding did not recur and she was discharged on September 18. Readmitted on September 26 and discharged again as not in labor on October 1. Readmitted for the third time on October 18 and delivered a normal full-term living child on October 19 with low forceps. Placenta was normally placed. Discharged after an uneventful puerperium on October 22.

CASE 5.—Mrs. R. S., aged twenty-nine, para i, gravida ii, was not a prenatal clinic patient. She was first admitted to the hospital on Aug. 26, 1935, with a history of uterine bleeding. A cystogram which was doubtful, due to the prematurity of the fetus, was made on August 27. She was discharged from the hospital and was readmitted on September 23 with a history of having had one attack of bleeding during her interval at home. On September 23 she had been awakened



Fig. 3.—Mrs. R. S., aged twenty-nine, para i, gravida ii. There is a definite increase in the separation of the fetal head and the bladder beginning at about the midline and gradually increasing toward the left side. A diagnosis of left lateral placenta was made and confirmed.

from sleep to find that she had bled enough to saturate her bedclothing. She came immediately to the hospital and was still bleeding on admission. Physical examination revealed her to be in low-grade shock with a blood pressure of 55/40. Hemoglobin 30 per cent. The fundus uteri was halfway between the umbilicus and xiphoid. There were no uterine contractions. Immediate transfusion of 500 c.c. citrated blood given with routine shock treatment. Reaction was good and about twelve hours after admission the blood pressure had risen to 100/60. Cystogram was done as soon as it was possible to move the patient and a diagnosis of probable placenta previa was made (Fig. 3). Low cesarean section was done under local anesthesia and a living premature child was delivered, which died about twelve hours after delivery. The placenta was definitely laterally placed. Convalescence of the mother was uneventful except for a postoperative bronchitis which cleared up without difficulty. She was discharged on October 4 to the care of her private physician.

CASE 6.—Mrs. R. S., aged twenty-five, para i, gravida ii. Last menstrual period on Dec. 18, 1934. First seen in the prenatal clinic on July 23, 1935. Pelvic measurements were adequate. She was admitted to the hospital on September 24



with a history of bleeding without labor pains for seven to ten days before admission. Flow was similar to that of a normal menstruation. On September 23 she passed "something" described as a part of the placenta by a local physician. Membranes were intact. No labor pains. Physical examination was negative. Fundus was three fingers below the xiphoid. Fetal head was above the pelvic brim. Fetal heart tones were in the right lower quadrant. Position right occiput anterior. The placental souffle could be auscultated just above the left inguinal ligament. The uterus felt rigid in spite of the fact that the patient complained of no pain. Cystogram was done soon after admission and was diagnosed as placenta previa (Fig. 4). Laparotrachelotomy was done on September 25 under local and nitrous oxide anesthesia, with delivery of a living child. Placenta was found to be central in type occluding the internal os. Convalescence of the mother was satisfactory. She was discharged on October 4.

CASE 7.—J. M. D., aged twenty-seven, para iv, gravida ix. Last menstrual period on Jan. 27, 1935. First clinic visit on Sept. 6, 1935. Pelvic measurements adequate. Prenatal period uneventful, except for some edema of the feet and slight visual disturbances, until October 13 when she began having uterine bleeding. She stated

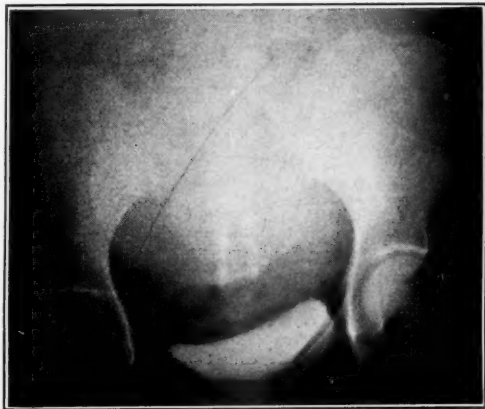


Fig. 4.—Mrs. R. S., aged twenty-five, para i, gravida ii. The separation of the bladder and the fetal head is approximately the same across the entire top of the bladder. However, the measurement ranges from 3 to 4 cm. as contrasted to that of the normal of 1 to 2 cm. With the history and physical findings coordinating with the cystogram, a diagnosis of central placenta previa was made.

that she was asleep and was awakened to find she had soaked her bed. Bleeding continued intermittently until October 18 when she came to the clinic. Cystogram was made before admission to the hospital and was suggestive of placenta previa. On admission her physical examination was negative except for a slight edema of the feet. Blood pressure 126/76. Fundus was three fingers above the umbilicus. Head engaged in the pelvis. Fetal heart tones in the right lower quadrant. Position right occiput anterior. The placental souffle was heard in both flanks over the inguinal regions, but was greater on the left. Laparotrachelotomy under gas anesthesia on October 18 and an eight months' child delivered. The placenta was found to be partially occluding the internal os. Postoperative convalescence uneventful. Discharged on October 26.

CASE 8.—I. H., aged thirty-six, para iv, gravida v. Last menstrual period on May 4, 1935. First seen in the prenatal clinic on Oct. 14, 1935. Original examination at the clinic was negative. Pelvic measurements adequate. Prenatal period uneventful until Dec. 3, 1935, when she had slight vaginal bleeding. She was ad-

mitted to the hospital, and was treated with opiates, rest, etc. The bleeding checked and she was discharged after two days. She remained in bed at home for one week. On December 30 she had a sudden large hemorrhage followed by slight bleeding daily until Jan. 3, 1936, when she again had a sudden gush of blood followed by laborlike pains which lasted eight hours. She had had no pains for twelve to fourteen hours before admission. On admission physical examination was negative. Blood pressure 124/84. Fundus was at the xiphoid. Vertex presentation. Position right occiput anterior. Fetal heart tones high on the right. There were blood clots in the vagina. Hemoglobin 58 per cent. Cystogram was made and a diagnosis of placenta previa was suggested even though the head was high. She was observed until January 6 when she was given a transfusion of 550 c.c. of citrated blood. Laparotrachelotomy was done two hours after the transfusion, and a full-term living child was delivered. Placenta was found to be lateral in type. Convalescence uneventful. Discharged on January 16.

CASE 9.—E. L., aged twenty-two, para i, gravida ii. Last menstrual period on May 6, 1935. First seen in the prenatal clinic on Sept. 27, 1935, at which time the fundus was 17 cm. above the top of the symphysis. Fetal heart tones were not heard. There was slight vaginal bleeding at that time. Two weeks later, after rest in bed, vaginal spotting was still present. The fetal heart tones were present in the left lower quadrant of the abdomen. Placenta previa was suggested as a possible cause of the bleeding. Patient continued spotting intermittently until October 19. On December 20 the placental souffle was definitely heard over the right inguinal region. She was admitted to the hospital on December 29 and a cystogram made on December 30—head too high for accurate diagnosis. Discharged on Jan. 3, 1936. Readmitted on February 6 with a history of slight bleeding on one occasion since her previous admission. On examination there was some hyperemia of the nasal mucosa with a few crackling râles at the left base. Blood pressure 110/78. Fundus uteri two fingers below the xiphoid. Head floating over the pelvic brim. Fetal heart tones in the left lower quadrant. Position left occiput anterior. No labor pains. Cystogram was repeated on February 8 and a diagnosis of placenta previa was made. Laparotrachelotomy was done on February 9 under local and gas anesthesia with delivery of a living child. Placenta was partially occluding the uterine os. Convalescence was satisfactory except for a slight wound infection at the upper angle of the incision. Discharged on February 22.

In this series of nine cases a positive diagnosis of placenta previa was made in seven. The policy of the attending staff of the hospital has recently been to deliver patients of this type by cesarean section, which has given excellent opportunity to study and confirm the cystographic findings. In all of the patients who were delivered by section, the placenta was found to be either partially or completely occluding the internal uterine os. However, it is not intended here to discuss the treatment of placenta previa, but rather its diagnosis. We feel that any procedure that leads to a more correct diagnosis is valuable regardless of the method of delivery of that case.

Needless to say there have been equally as many patients with abnormal bleeding during the last trimester of pregnancy in which the diagnosis of placenta previa has not been made cystographically. These patients have been treated conservatively and subsequently delivered without difficulty. When the classical symptoms and physical findings of placenta previa are present and there is the added suggestion of the

condition found on x-ray, there should be no hesitancy in making the diagnosis. Conversely, if there are symptoms of previa which are not confirmed by the cystogram, observation of the patient can usually be made without as grave apprehension as usually accompanies hemorrhage.

#### SUMMARY

1. The technic of the cystogram is given and the criterion of diagnosis of placenta previa.
2. Presentation of nine cases which were studied as suspected placenta previa and in which the positive diagnosis was made in seven of the cases by use of the cystogram.
3. The delivery findings in the seven cases confirmed the diagnosis of either a lateral or complete placenta previa.
4. There was no maternal mortality.
5. Two of the children died after delivery, one from prematurity and the other from bilateral atelectasis.
6. The method of cystographic diagnosis is not suggested as an infallible one, but rather is to be used in conjunction with the history and suggestive physical findings of placenta previa.

Expression of appreciation is made to Dr. Karl Kesmodel and Dr. J. A. Meadows of the radiological staff of the Hillman Hospital for their kind assistance in the study of the x-ray plates.

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2801 ENSLEY AVENUE

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Lenner reports two cases of hematoma of the rectus muscle in women. In the first patient a diagnosis of fibroid uterus had been made and in the second the diagnosis made was infected ectopic pregnancy. Both women had hemorrhages in the rectus muscles. A review of the literature revealed 72 cases of hematoma of the rectus muscle in women. Of these, 15 occurred in connection with pregnancy or labor and 57 in nonpregnant women. In the nonpregnant individuals severe coughing seemed to play an important rôle, especially in elderly women. In most instances, the hemorrhage was located in the right lower quadrant. The correct diagnosis was seldom made. Of the 15 cases occurring during the pregnant state, 11 occurred during the latter part of gestation, and in four the hemorrhage took place during labor or the early puerperium. The prognosis is favorable. In mild cases conservatism gives satisfactory results, but in serious cases an operation must be performed.

J. P. GREENHILL.

## BLOOD PHOSPHATASE IN PREGNANCY

THEODORE MERANZE, M.D., DAVID R. MERANZE, B.S. (Chem.), M.D., AND  
MAURICE M. ROTHMAN, M.D., PHILADELPHIA, PA.

*(From the Department of Obstetrics and the Laboratories of the Mount Sinai Hospital)*

THE special needs of the maternal organism in pregnancy have been recognized for a long time. It has been realized that the developing fetus imposes definite dietary requirements upon the mother. If these dietary constituents are not adequately supplied, deficiency states in either the mother or fetus, or both, may result. Support for this belief has been found in the altered chemical findings of the blood in the parturient woman, upon balance experiments in the latter months of gestation and from animal experimentations.<sup>1-6</sup> As a result many physicians routinely alter the diet of the mother, and especially increase her intake of the mineral constituents, particularly calcium and phosphorus. The occurrence of rickets in the newborn and in infancy is believed by a few investigators to be due in some instances to a deficient diet in the mother. In the past, cases of intrauterine rickets have been reported.<sup>7, 8</sup> Rickets in the newborn and shortly after birth is not uncommon.<sup>9, 10</sup> By the administration to the mother of an adequate mineral diet and a sufficient quantity of vitamin D some clinicians have observed an improved state of general health in the parturient woman and an absence of evidence of rickets in the newborn.<sup>5</sup>

During pregnancy and lactation the problem is therefore twofold: (1) maintenance of the health of the mother and (2) the maintenance of optimal conditions for the development of the fetus. The mother during pregnancy supplies all the substances necessary for the growth of the fetus. These substances the mother either obtains in her diet, synthesizes from her diet, or supplies to the fetus by depletion from her own tissues. If the maternal diet is deficient, this depletion may result in varying degrees of ill health of the mother, and, ultimately, of the fetus. Some of the commoner deficiencies in the maternal diet during pregnancy appear to be in vitamins A and D, calcium, phosphorus, iron, and iodine. An abundance of both vitamin D and calcium is essential for the proper development of the bony skeleton and teeth of the growing fetus. The maternal stores of vitamin D are small.<sup>11</sup> Her bones, however, constitute a large depot of calcium and phosphorus. These substances she can transfer to the developing fetus. If the maternal diet is deficient in calcium and phosphorus, the drain may result in osteomalacia, or, more commonly, dental caries in the mother.<sup>7, 11, 12</sup>

In recent years the study of the enzyme phosphatase has contributed considerably to our understanding of normal and pathologic bone formation.

This enzyme was first isolated by Robison in 1923 from ossifying cartilage.<sup>13</sup> He believed at that time that the enzyme played a dominant rôle in the process of ossification. This view has been accepted by subsequent workers.<sup>14, 15</sup> Numerous investigations have shown, moreover, that this enzyme is elevated in the blood above the normal in several groups of conditions, such as certain bone diseases,<sup>15</sup> jaundice other than hemolytic,<sup>16, 17</sup> and in many instances of malignant involvement of the liver.<sup>18</sup> In bone disease it has found its greatest application in the study of Paget's disease and rickets.<sup>19</sup> In rickets and in what is considered to be its adult equivalent, osteomalacia, the blood phosphatase is elevated in the active and progressive phases, and approaches normal as the disease state is brought under control. In rickets it is important to note that an apparent lag in the return of the blood phosphatase to normal during successful therapy is observed. Several recent writers on the subject feel that the blood phosphatase levels reflect more sensitively the status of bone metabolism in the body than does any other available test at the present time.<sup>15, 19</sup>

In jaundice the phosphatase values have been found elevated in all forms except those of the hemolytic type. Some workers believe that the determination of this enzyme in the blood offers the best single means of differentiating between cases of obstructive and nonobstructive jaundice.<sup>16, 17</sup> It has been suggested that the elevation in these cases of jaundice may be due to the altered carbohydrate metabolism accompanying the liver changes present, and that the elevation in these instances does not, therefore, reflect the same disordered bodily mechanism as is present in bone dyscrasias.<sup>20</sup>

It has occurred to us that the study of the blood phosphatase levels in parturient women might provide some additional insight into the bone metabolism in pregnancy. Accordingly, blood phosphatase values were determined in a large series of pregnant women.

At the present time several methods are used to determine the phosphatase activity of the blood.<sup>15, 16, 21</sup> These are essentially similar in principle. They consist in measuring the phosphorus set free as inorganic phosphate when the enzyme present in the blood is allowed to act on a phosphoric acid ester substrate under standard conditions. Unfortunately there is at present no general agreement in reporting results so that it is difficult to convert one group of findings into another. We have used in our work a slight modification of the method employed by Roberts.<sup>16</sup> This method is as follows: The determinations are made on fasting blood. Two cubic centimeters of plasma (citrated blood) is mixed with 2.3 c.c. of distilled water and 0.7 c.c. of N/10 sodium hydroxide. This produces a pH of approximately 8.9. To this is added 1 c.c. of a 1 per cent solution of sodium beta-glycerophosphate. The mixture is then incubated at 37.5° C. for two hours, after which its inorganic phosphorus content is determined by the method of Fiske and



Subbarow. At the same time the initial phosphorus content of the plasma is determined using another 2 c.c. of the original blood plasma. Both of these values are determined in mg./100 c.c. of blood plasma. The difference between these two values represents the number of milligrams of inorganic phosphorus liberated by the enzyme, phosphatase, from the substrate under the above conditions. Each milligram thus obtained is expressed as units of phosphatase per 100 c.c. of blood plasma. According to this technic we have found the normal values for adults to range up to 6 units, while for children values up to 15 units are to be considered normal.

TABLE I. PLASMA PHOSPHATASE IN PREGNANCY

Table showing the range and average values of plasma phosphatase, and average blood calcium and phosphorus values found in 201 cases of pregnancy. \*Studies done during active labor. \*\*Per 100 c.c. blood plasma.

Month of Gestation	3rd	4th	5th	6th	7th	8th	9th	Before*	Cord Blood	Days post-partum		
No. of estimations	13	9	32	38	47	62	57	35	15	18	19	17
Units of phosphatase - Average**	2.08	2.45	3.02	3.36	4.79	8.33	10.35	12.53	4.01	10.09	6.38	6.90
Range in units of phosphatase**	1.64 to 3.04	1.28 to 3.90	1.30 to 4.44	1.40 to 4.48	2.16 to 8.58	2.40 to 17.80	5.66 to 24.48	5.98 to 22.60	1.84 to 6.64	8.48 to 17.04	3.16 to 13.44	3.64 to 12.64
Blood phosphorus Average-mgm./100 cc. blood plasma	3.33	2.82	3.14	3.10	3.09	3.12	3.07	3.15	5.00	3.88	3.76	3.91
Blood calcium Average-mgm./100 cc. blood plasma	18 cases = 11.50 mgm.				44 cases = 10.44 mgm.			7 cases = 10.60 mgm.		12 cases = 11.19 mgm.		
Graphic presentation of average phosphatase values	13 units											
	12 "											
	11 "											
	10 "											
	9 "											
	8 "											
	7 "											
	6 "											
	5 "											
	4 "											
	3 "											
	2 "											
	1 "											

As we have stated before, believing that the determination of this enzyme in the blood might prove to be a sensitive and early indicator of dysfunction of maternal or fetal bone metabolism, we have made plasma phosphatase determinations in a series of 201 parturient women in the various months of pregnancy. The results are shown in Tables I, II, and III. In all we have made 347 phosphatase determinations. In many instances we have repeated the determinations in the same individual during succeeding months of gestation. A few determinations in the first ten days following the delivery are also listed in Table I. We have in all instances done simultaneous blood phosphorus determinations and in many instances blood calciums. In passing it may be stated that we have noted no constant or suggestive relationship between the blood calcium and phosphorus estimations and the simultaneous blood phosphatase values. Mull and Bill<sup>22</sup> have shown that in a series of pregnant

white women there is a seasonal variation in the calcium and phosphorus values, the values during the months of January to May averaging less at every stage than those during the remaining seven months. In Table II we have therefore listed the phosphatase values according to the sex of the newborn and to the season of the year of their birth.

## DISCUSSION

A study of Table I discloses that the blood phosphatase values during the first six months of pregnancy lie within normal limits. The average values in the seventh month appear significantly different from those of

TABLE II. RELATION OF PLASMA PHOSPHATASE TO SEX OF CHILD AND SEASON OF YEAR OF BIRTH

SEASON OF YEAR OF BIRTH	MONTH OF GESTATION	AVERAGE PLASMA PHOSPHATASE UNITS/100 C.C. BLOOD PLASMA			AVERAGE PLASMA PHOSPHORUS MG./100 C.C. BLOOD PLASMA	
		MALE	FEMALE	BOTH	MALE	FEMALE
April to October	8th	7.92	7.65	7.84	3.25	3.02
	9th	9.27	11.06	10.16	3.14	3.00
	Before*	12.09	13.19	12.64	3.15	3.30
November to March	8th	8.73	8.33	8.50	3.14	3.12
	9th	11.17	9.89	10.53	3.07	3.08
	Before*	13.14	11.73	12.43	3.16	3.00

\*Taken while patient was in labor.

TABLE III. PLASMA PHOSPHATASE OF UNUSUAL CASES

AGE OF MOTHER	NUMBER OF PREGNANCIES	MONTH OF GESTATION	UNITS OF PLASMA PHOSPHATASE/100 C.C. PLASMA	REMARKS CONCERNING PRESENT PREGNANCY
36	1	Before*	22.36	Triplets, 1 dead
35	3	Before*	8.08	Macerated dead fetus
44	1	8th	5.98	Premature, died
18	1	9th	11.60	Macerated dead fetus
34	2	9th	11.60	Living twins
25	3	9th	13.00	Living twins
27	3	9th	13.38	Living twins
19	1	9th	11.90	Living twins
27	2	9th	12.60	Living twins
24	2	9th	9.72	Living male, preeclamptic Toxemia
34	8	Before*	9.80	Living twins
32	3	9th	11.49	Preeclamptic toxemia
35	5	Before*	14.56	Living male
27	5	9th	8.07	Preeclamptic toxemia
37	3	Before*	9.72	Living female
29	3	9th	8.72	Preeclamptic toxemia
32	2	9th	11.13	Living male, hypertension
37	3	Before*	12.96	Living male, hypertension
24	4	Before*	12.52	Living female, hypertension
45	1	9th	14.74	Living female, hypertension

\*Taken while patient was in labor.

the sixth month, and here for the first time individual values above normal are obtained. In the eighth and ninth months the values become definitely elevated, averaging 8.33 and 10.35 units, respectively. Only exceptionally in these two months is a value obtained which lies within the range of normal for the nonparturient woman. During labor the values average at even higher levels, 12.53 units. Postpartum the phosphatase values fall rather abruptly, reaching average levels of 6.9 units at the end of ten days. This latter value is still above normal, and the group contains a considerable number of cases with readings markedly above normal. The high levels found in the last months of pregnancy are in general agreement with the reported findings of Cayla and Fabre,<sup>23</sup> whose work came to our attention after our own investigations had been completed. These workers studied a small group of parturient and nonparturient women. They found that the average blood phosphatase for the nonparturient women by their technic was 16 units per liter of blood. In their group of parturient women of approximately the same age levels they obtained average blood phosphatase values of 36.4 units per liter of blood in the seventh month of gestation, and average combined values of 38.8 units per liter of blood for the eighth and ninth months.

A few studies of blood phosphatase in the newborn and in infancy are available. Stearns and Warweg<sup>24</sup> in a thorough study of the blood phosphorus, calcium and phosphatase from birth to maturity found that the plasma phosphatase at birth was low and rose abruptly to a maximum during the first month. Bodansky<sup>25</sup> in a later study on newborn puppies found high values, averaging about 40 units (normal 1.5 to 3 units for adult dogs) at birth and for about four hours thereafter.

We have done 15 phosphatase determinations on cord blood (Table I). These values average 5.00 units, with a range of from 1.84 to 6.64 units, values that are lower than the normals for children. The average for children is about 7.5 units and ranges up to 15 units by our technic.

Blood phosphorus determinations were done on all cases. On the whole these values remained essentially constant throughout, though at a slightly low normal level. No significant difference was observed in the blood phosphorus values of the last two months of gestation. The relatively high phosphorus values in the cord blood and the generally elevated phosphorus values in the postpartum period are noteworthy.

From the results listed in Table II it would appear that there is no significantly consistent difference between the phosphatase values in the blood of women bearing males and those bearing female children. Nor does the season of the year of birth appear to affect significantly the blood phosphatase or phosphorus values. Our work with the blood calcium has been too inadequate for analysis in regard to seasonal variations. Nor were the weights of the delivered fetuses or the degree of gravidity of the mother significantly correlated with the phosphatase values.

In Table III we have listed the findings in those cases of pregnancy which deviated from the usual in some respect. Though not necessarily significant, it is interesting that with one exception the maternal blood phosphatase values of the cases of twin pregnancies were above average and that of the instance of triplets decidedly above average. The other conditions listed did not appear to affect the phosphatase findings significantly.

The rise in the blood phosphatase in pregnancy, particularly in the last three months, may be variously interpreted. It is clearly established that the process of ossification in the developing fetus is at its height in these last three months. Givens and Macy<sup>26</sup> have shown by a series of laborious analyses that the greatest fetal demand for minerals occurs during the last three months of gestation. It can therefore be concluded that the last trimester is the period of greatest activity in fetal ossification and therefore presumably the period of greatest phosphatase need. That this fetal need exists is supported by the finding of high blood phosphatase values in infancy and childhood, the periods of great activity of bone formation.<sup>24, 25</sup> However, the low values found by us in the cord blood, figures which represent composites of maternal and fetal values, may indicate that the fetus, in utero at least, is unable to provide sufficient amount of the enzyme phosphatase for its needs, and that the high values found in the maternal blood during the last months of gestation may represent a successful compensatory response in the mother.

Or are these elevated values to be regarded as delicate indices of potential or actual preclinical disorders in bone metabolism in either mother or fetus? Except in normal periods of increased ossification in infancy and childhood, blood phosphatase values above the accepted normal usually indicate abnormal or immature ossification, as in Paget's disease and rickets. That the last three months of pregnancy are crucial for the maintenance of the integrity of the bone metabolism of the mother is evident from the numerous clinical reports of dental caries, of reports of osteoporosis, and the occasional occurrence of maternal osteomalacia. This period is equally critical for the fetus. We have already called attention to the existence of cases of fetal rickets. Do therefore the elevated blood phosphatase values represent a pathologic or potentially pathologic state of bone metabolism in mother or fetus?

Since the phosphatase values of the cord bloods were low, the high maternal phosphatase values, prior to delivery, can be interpreted only as being predominantly of maternal origin. Stearns and Warweg<sup>24</sup> find low values in the newborn immediately after birth. Hence the fetus appears to be elaborating very little of the enzyme phosphatase, and, in utero, apparently is dependent upon its mother for its requirement of this enzyme. It is possible that the normal development of the fetus is dependent upon an adequate supply of the enzyme phosphatase by the mother and that an inadequate supply of this enzyme in utero

will lay the groundwork for the development of rickets in the fetus and infant. At the present time we are engaged in a series of investigations designed to throw light on this question.

Finally, we cannot attribute the elevation of the blood phosphatase in the last two months of pregnancy to the coexistence of liver disease or jaundice in the mother. None of our patients were jaundiced, nor were they suffering from any of the other diseases known at the present time to be associated with an elevation of the blood phosphatase. It will also be seen from a study of Table III that in the few cases with hypertension, and preeclamptic toxemia, the blood phosphatase values did not vary significantly from the average.

#### SUMMARY

1. Blood phosphatase determinations were done on 201 cases of normal pregnancies representing all of the months of gestation.
2. The average blood phosphatase values were found to be definitely higher than normal in the last two months of pregnancy and during labor.
3. Relatively low phosphatase levels were found in a small number of determinations in cord blood.
4. There was no significant relationship observed between the blood phosphatase levels and the sex of the newborn or the season of the year of their birth.
5. The possibility that the blood phosphatase levels may reflect normal or early abnormal phases of bone metabolism in the mother or fetus is discussed.

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## AN ANALYSIS OF 482 CESAREAN SECTIONS IN PRIVATE PRACTICE

JAMES V. CAMPBELL, M.D., OAKLAND, CALIF.

MUCH discussion has been elicited because of the increasing number of sections being done throughout the country. There is no doubt that the indications have been liberalized. Many of us have yielded to the pressure brought to bear by patients who have no intention of having more than two or possibly three children and who do not propose to lose the present incumbent, as it were, during the course of a difficult labor. To go into all the sociopsychologic bypaths which have led to this current frame of mind is not my intention.

We are confronted with the fact that many men are operating who are not qualified to judge when operation is indicated nor trained to operate. This partially accounts for the excessively high maternal mortality following cesarean section which is reported for this State and for the country as a whole. The present trend for operative deliveries is rapidly becoming the recognized procedure, as far as the laity is concerned, and the general practitioner is compelled to keep step. All of us hear patients say that they would much rather have a cesarean because it is so much easier, and they are sure to have a baby to show for their time, effort, and monetary output.

The present report is given in order to analyze cesarean section under more favorable conditions. First: it deals with a so-called higher class of patients well above clinic or even general practice average; second: practically all of the patients have had adequate prenatal care; third: the operating has been done by well-trained obstetricians with a uniformity of technic and training. Furthermore there are more cesarean sections followed by hysterectomy in this series than in any report I have seen to date.

This series of sections is taken from a group of 4,979 deliveries of patients six months pregnant or over, a cesarean incidence of 9.68 per cent as compared with the general hospital percentage of 2.9 per cent as given by Dr. Maxwell's report of three years ago. In this group are listed 404 classical sections, 73 with hysterectomy, 1 low cesarean, and 4 vaginal hysterotomies. The last five will be included in the general average but will not enter the general discussion. The low section was done for a relative disproportion, with no mortality. The 4 vaginal sections were done for the following reasons:

1. Premature rupture of membranes with uterine inertia at six months.
2. Premature separation of the placenta at six months.

3. Preeclamptic toxemia at six and one-half months developed postpartum toxic psychosis with recovery.
4. Preeclamptic toxemia.

The first three each accounted for a fetal death. There was no maternal mortality.

TABLE I

INDICATIONS	CLASSICAL		CLASSICAL WITH HYSTERECTOMY	
	PRIM.	MULT.	PRIM.	MULT.
1. Contracted pelvis	121	8	-	-
2. Previous section	-	72	-	38
3. Disproportion	61	7	-	-
4. Elective	41	7	2	2
5. Toxemia	31	1	-	-
6. Previous difficult delivery	-	17	-	7
7. To sterilize	1	11	-	16
8. Placenta previa	4	4	-	1
9. Abruptio placentae	3	2	1	1
10. Fibroids	2	3	4	1
11. Pelvic injury	4	-	-	-
12. Cardiac disease	3	1	-	-
	271	133	7	66
	404—84%		73—15.3%	

In listing the definite reasons for cesarean, it must be borne in mind that in some 60 instances there were contributing factors which were of secondary importance, but nevertheless convinced the operators of the advisability of the elected procedure.

#### CONTRACTED PELVES (129 CASES)

An arbitrary standard of measurements was set in order to give a definition of contracted pelvis. Any patient whose measurements were below this standard was listed. Funnel pelvis accounted for 100 cases, flat pelvis for 21 cases, and justminor for 8.

In this group were 121 primiparas of whom 18 had had a test of labor. Of the 8 multiparas, 3 were allowed a test of labor. The classical operation was done in every instance. No maternal mortalities were resultant in this group but there occurred 4 fetal deaths due to: (1) Congenital heart, 2; (2) question of cerebral hemorrhage, death two days postpartum; (3) no cause known, baby died one month postpartum. One set of twins was delivered.

There were 4 patients who developed serious morbidity; 1 developed a thrombophlebitis; 2 had acute mastitis necessitating drainage in one; and one patient had an active pyelitis with metastatic abscesses in the neck. Induction of labor had failed.

In a series of 4,142 women who had vaginal deliveries by the same operators, there were 25 fetal deaths (19 per cent) following difficult forceps deliveries. These were patients who had no other contributing factors such as toxemia, etc., and who were at term. With this knowledge in mind, and in the interests of the child, the operators were more prone to section the woman with a contracted pelvis without any test of labor.

#### PREVIOUS SECTIONS (110 CASES)

This group consisted of 110 patients, 72 of whom had the classical operation and 22 of the 72 had tubal ligation. Two individuals were allowed a moderate test of

labor but made no progress. One mother died of intestinal obstruction nine days postoperative. Her previous surgery consisted of a classical cesarean which was done for contracted pelvis.

No fetal deaths occurred. Two patients developed a moderate postoperative fever with good recovery; two had an acute mastitis without further complications; and one had perineal abscesses due to infected hemorrhoids. Thirty-eight sections with hysterectomy were done with no deaths and no serious morbidity. There was one set of twins.

It is interesting to note that of the 60 patients who had had previous sections and were sterilized either by tubal ligation or fundectomy, 51 elected to be sterilized following only one previous cesarean section. Granted that a certain number of the sections with hysterectomy were done because of adhesions, still the tendency was to limit the family to two children.

#### TO STERILIZE (28 CASES)

Of the patients sterilized, 12 had tubal ligation with no deaths and only one developed a moderate postoperative fever. The remaining 16 individuals had cesarean section and amputation of the fundus with no fetal, but one maternal death. No known cause could be found why she should die. Her first baby was lost following a difficult forceps delivery and she requested sterilization.

#### RELATIVE DISPROPORTION (69 CASES)

Of those individuals classified in this group, all had normal pelvic measurements but were sectioned for one of two reasons: first, failure of the presenting part to engage due to postmaturity, hydramnios, etc.; second: when, following engagement, there was no progress due to cervical dystocia, ineffective uterine contractions or other local causes.

Of the 69 patients sectioned for disproportion, 61 were primiparas, and 24 of these had a test of labor varying from six to thirty hours. Seven of the 8 multiparas were given a test of labor. No maternal deaths occurred but one baby died of congenital heart. All of the operations in this group were of the classical type. Morbidity was noted 3 times, twice when the abdominal wall became infected and partially separated; and once when the patient developed some elevation of temperature. An attempt to apply forceps had been made prior to operation in the last instance.

The great majority of individuals who had contracted pelvis or a relative disproportion and were given a test of labor, were watched very carefully in the hospital. Operation was advised before the mother became too exhausted or the chances for the baby were unduly diminished.

#### ELECTIVE (52 CASES)

Elective cesarean section was based upon the following causes:

Elderly primiparas	21
Personal request	12
Prolapsed cord	4
No cause given	4
Hematuria	2
Uterine inertia	2
Acute massive edema of external genitalia	2

One each of the remainder:

- Elderly primipara, transverse position, dextrotorsion of the uterus
- Transverse position, cervical displacement from previous operation
- Tuberculous hip with ankylosis
- Prolonged sterility treatment
- History of endometriosis

Of this group 10 were multiparas. Two elderly primiparas had hysterectomy. Two fetal deaths occurred and one mother died of a postoperative ileus. Three patients developed secondary wound infections and one had a moderate postpartum hemorrhage.

#### TOXEMIA (34 CASES)

What to do about the toxic patient is always a debatable subject. Of 4,624 deliveries there were 168 cases of toxemia varying from a mild albuminuria or slight rise in blood pressure to the fulminating eclamptic patient. Approximately 1 out of 3 of these patients was sectioned. This group was divided into the eclamptic and the preeclamptic type patient, depending upon the presence or absence of convulsions or coma. There were 12 eclamptic patients, all primiparas, with 2 infant deaths at six and six and one-half months and no maternal deaths. The preeclamptic patients were 22 in number, with 20 primiparas, 2 of whom had vaginal hysterotomies. Three fetal deaths occurred: one premature at six and one-half months following vaginal hysterotomy and 2 at seven and one-half and eight months, respectively, following the classical operation. Two sets of twins were delivered. The recorded morbidity ran rather high in this group and was characterized by the large number who developed postoperative convulsions, 9. Other complications were: 1 infected wound, 1 postoperative ileus with recovery, and 1 temporary anuria.

The fact that 4 out of 5 of the fetal deaths were due to prematurity associated with toxemia would seem to substantiate the idea that a vaginal delivery of some type, even though destructive to the fetus, should be done on toxic patients who are not near term. The consideration of the baby is distinctly of secondary importance in this instance.

#### PREVIOUS DIFFICULT DELIVERY (23 CASES)

There were 23 patients who had one or more very difficult vaginal deliveries with the loss of the babies and some with severe lacerations. Sixteen classical operations and 7 sections with fundectomy were done, with one set of twins. In one instance both the mother and the baby died. Maternal death was due to cerebral thrombosis eighteen days postpartum. She was given a test of labor but there was failure of the presenting part to engage. Though the baby was at term it was stillborn. A number of rather serious sequelae followed operation in this series of cases: (1) Infected abdominal wound; (2) acute dilatation of the stomach; and (3) postpartum toxic psychosis with recovery.

#### PLACENTA PREVIA (9 CASES)

Of 20 cases of placenta previa encountered in 4,624 patients, 9 were sectioned, 8 by the classical method and 1 with hysterectomy. There were 4 primiparous and 5 multiparous women with no maternal deaths. Two babies died of prematurity at six and six and one-half months.

#### ABRUPTIO PLACENTAE (9 CASES)

Premature separation occurred 22 times all told. Cesarean operation seemed indicated and was done on 9 patients, 5 classical, 2 with amputation of the fundus, and 2 vaginal hysterotomies. Of these, 4 women were in their first pregnancy. No mother died but two babies did, both prematures operated by cesarean section with fundectomy and vaginal section. There was no untoward morbidity in either of the hemorrhage groups.

#### FIBROIDS (10 CASES)

Of the 10 women who had fibroids, 5 had a hysterectomy and the remainder, 2 primiparas and 3 multiparas, the classical operation with myomectomy. No mortalities were recorded though one patient acquired a postoperative phlebitis and one was in rather severe shock followed by good recovery.

## MISCELLANEOUS (8 CASES)

There were 8 other patients, 7 primiparas and 1 multipara, who complete the list of cesarean sections. Four of these had had pelvic injuries which made normal delivery very questionable and 4 were severe cardiac patients, one of which was kept in bed for two months prior to delivery. All had the classical operation. One cardiac patient was sterilized by tubal ligation. No mortality or morbidity occurred.

## TYPES OF OPERATION

The distribution of the types of operation is of interest. Of 404 classical sections 271 were primiparous and 133 were multiparous women. On the other hand only 7 of the 73 cesarean sections with hysterectomy were primiparas.

Incidental operations performed were as follows: tubal ligation 41 (5 primiparous and 36 multiparous women); appendectomy, 57; myomectomy, 13; hernia, 2; bilateral salpingo-oophorectomy, 1; left oophorectomy, 1.

## MATERNAL DEATHS

In reviewing the maternal deaths in this series of 482 cesarean sections, there were 4 deaths or 0.826 per cent. Listing these cases:

1. Classical section on an elderly primipara with heavy muscles but normal measurements, death due to postoperative ileus (question of obstruction).
2. Classical section because of previous section which had been done for funnel pelvis, death due to intestinal obstruction.
3. Cesarean section with fundectomy in order to sterilize because patient had had two difficult deliveries before, though normal pelvis, and did not want any further pregnancies, no known cause was made out for her death.
4. Classical section on a patient who had previously lost two babies following difficult breech deliveries, death due to cerebral thrombosis, the first attack nine days postpartum and the second attack eighteen days postpartum.

Further analysis shows that among these deaths there were no cases in which any accessory operation had been done. Even where the accessory operation could be considered a contributing factor, I have been unable to find any increased morbidity. As a whole, it was noted that the patients who had cesarean section with hysterectomy tended to have a quieter and easier convalescence.

In those patients who were to be sterilized following previous section, cesarean section with amputation of the fundus was, in a number of instances, selected because of numerous adhesions. This no doubt prevented further adhesions and possible obstruction. Rupture of the uterine wall did not occur.

In this report all the referred cesarean sections were isolated in order that some comparison of the results might be made. They are not included in the previous figures. The 76 individuals of the referred group had been under the care of some outside physician, who in turn brought them for consultation. In this group are found 4 deaths (5.3 per cent mortality) and one patient who died of fulminating pneumonia. A postmortem cesarean section was done, in vain, to save the baby. Three of the other four were extremely sick before operation:

1. Vaginal hysterotomy, patient had been in a semiconscious state for one week before operation. Bag induction was attempted at six and one-half months without success. She died a few hours postoperative without gaining consciousness.



2. Classical section because of a fulminating tuberculosis, patient died five days after operation.

3. Classical section because of endocarditis and to save labor; patient died eight hours postoperatively of cardiac failure.

4. Low cesarean section for relative disproportion; no cause known for death.

A review of the maternal deaths following vaginal deliveries (11 or 0.24 per cent) shows that the mortality represents a cross-section of maternal deaths due to be expected, i.e.: toxemia (2); cardiac disease (2); pelvic cellulitis (2); and one each of the remainder: hemorrhage from rupture of the uterine artery, acute pyelonephritis; fulminating pneumonia; pachymeningitis; and cause unknown. After a careful check on these cases there were none in which a cesarean section was indicated.

It will be noted that the deaths occurring in the controlled series of cesarean sections were not obstetric but surgical and that the death rate is about what one might expect following a series of abdominal operations which are not too radical. The referred patients more nearly represent the type of individuals and the problems encountered in clinical work.

#### FETAL DEATHS

In comparing the fetal deaths of the controlled group with those of the referred group we again find a difference in the cause of death.

In the group who were under constant supervision, there were 17 fetal deaths or 3.51 per cent. Ten were due to prematurity of which 8 were before the seventh month; 5 toxemia cases, 4 hemorrhage; 1 premature rupture of the membranes.

TABLE II. RELATION OF MATERNAL AND FETAL MORTALITY TO OPERATIVE INDICATION AND TYPE OF OPERATION

INDICATION	NUMBER CASES 482		MATERNAL MORTALITY 0.826%		FETAL MORTALITY 3.51%	
	CLASS.	CLASS. WITH HYSTEREC- TOMY	CLASS.	CLASS. WITH HYSTEREC- TOMY	CLASS.	CLASS. WITH HYSTEREC- TOMY
Contracted pelvis	129	0	0.0	0.0	3.10	0
Previous section	72	38	1.4	0.0	0.0	0
Disproportion	69	0	0.0	0.0	1.45	0
Elective	48	4	2.08	0.0	2.08	0
Toxemia	32	0	0.0	0.0	12.50	0
Previous difficult labor	17	7	6.25	0.0	6.25	0
To sterilize	12	16	0.0	6.25	0.0	0
Placenta previa	8	1	0.0	0.0	25.0	0
Abruptio placentae	5	2	0.0	0.0	0.0	50
Fibroids	5	5	0.0	0.0	0.0	0
Pelvic injury	4	0	0.0	0.0	0.0	0
Cardiac disease	4	0	0.0	0.0	0.0	0
Total	404	73	0.74%	1.36%	3.22%	1.36%

Three cases of congenital heart disease and 4 miscellaneous cases were reported: 1 of these died 1 month postpartum; 1 of enlarged thymus and atelectasis; 1 of possible cerebral hemorrhage; 1 stillborn following a test of labor with failure to engage.

Of the 78 babies in the referred group, there were 11 deaths (14.05 per cent). Five of these were listed as premature and four as stillborn, two due to placenta previa, one due to prolapsed cord with asphyxia and 1 whose mother was eclamptic. The miscellaneous group consisted of 2 babies; one died following a postpartum cesarean section and one died several days postpartum, cause unknown. Two sets of twins were delivered.

The vaginal deliveries of 4,142 patients over six months pregnant with 4,176 babies gave a maternal mortality of 11 or 0.24 per cent and a fetal mortality of 132 or 3.18 per cent.

#### SUMMARY AND CONCLUSIONS

1. A series of 482 cesarean sections in private practice is reviewed, 404 classical, 73 with hysterectomy, 4 vaginal and 1 low, with a maternal mortality of 0.826 per cent and a fetal mortality of 3.51 per cent.

2. With proper supervision, adequate judgment and good surgical technic the maternal mortality can be kept at the minimum to be expected when the abdomen is opened.

3. It would seem that more effort should be made to deliver the premature toxic patient vaginally inasmuch as the chances for the fetus are greatly diminished. Possibly vaginal hysterotomy might be employed more frequently.

4. When sterilization is indicated and there are numerous pelvic adhesions, cesarean section with fundectomy is to be seriously considered, since it aids in convalescence and prevents the formation of more adhesions.

5. Fetal death rate after eliminating the unavoidable deaths such as prematurity, congenital heart, etc., should be very low. In this series it was 1.25 per cent.

I wish to thank Dr. F. M. Loomis and Dr. J. W. Sherrick for the majority of the source material on which this paper is based.

2923 WEBSTER STREET

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**Kishori Mohan Pal:** Vesico-Vaginal Calculus in a Nullipara, Calcutta M. J. 30: 102, 1935.

A case of vesicovaginal calculus is reported in a fifteen-year-old, married, nulliparous Hindu girl, a vegetarian. No history of previous illnesses, and no family history of calculus. Chief complaints were vaginal discharge, incontinence of urine for one year, urinary frequency since five years, pain in lower abdomen and dyspareunia. Examination revealed a large calculus, partly visible at introitus, impacted in vagina, and continuous with a smaller portion in the bladder through a vesicovaginal fistula. Stone, removed by operation, weighed  $5\frac{1}{2}$  ounces and in its greatest portion was 7.5 cm. by 6.5 cm. This condition is a rarity. Only two cases of vesicovaginal calculus are reported in the literature; nine of vaginal type are described. The origin of the stone is questionable. Some believe it has a primary vesical formation, others a vaginal origin.

F. L. ADAIR AND S. A. PEARL.

## THE USE OF THE FEMALE BITTERLING AS A TEST FOR MALE HORMONE\*

ISRAEL S. KLEINER, PH.D., ABNER I. WEISMAN, M.D., AND  
DANIEL I. MISHKIND, B.S., NEW YORK, N. Y.

(From the Department of Physiology and Biochemistry of the New York Medical  
College and Flower Hospital)

### CRITIQUE OF RECENT EXPERIMENTAL WORK

RECENTLY there have been many contributions to the literature concerning the lengthening of the ovipositor of the female bitterling. It is generally conceded today<sup>1-5</sup> that this remarkable phenomenon, in which the female of this species of fish extrudes a long ovipositor, can be used as a definite biologic test for hormones found in urine.

We have found, in contradistinction to Kanter, Bauer, and Klawans and others who claim that the fish is a test for estrogenic hormone, that it actually is a test for the male hormones.<sup>6, 7</sup> Fleischmann and Kann, Ehrhardt and Kühn, Szusz, and other European investigators are responsible for the early work on the bitterling, while Kanter and others as well as ourselves were among the first in the United States to attempt to give the bitterling test medical significance. Kanter, Bauer, and Klawans in December, 1934, published a short article in the *Journal of the American Medical Association* entitled "A New Biologic Test for Hormones in Pregnancy Urine."<sup>8</sup> This application of the fish test to pregnancy immediately attracted a throng of investigators including ourselves, who very quickly proved that the bitterling test was not a pregnancy test.<sup>9</sup> Our stand has been corroborated by Gottlieb and others.<sup>10, 11</sup> In their second and most recent article entitled "Hormonal Studies with the Ovipositor Lengthening Reaction of the Japanese Bitterling,"<sup>4</sup> Kanter, Bauer, and Klawans suggest that we misinterpreted the statements in their first article. They insist that they had not intended to convey the impression that this is a test for pregnancy. However, the following quotation from their first paper will indicate that our interpretation had a real basis: "It was deemed advisable to run the fish test parallel to the Friedman test in order to determine the relative merits of the two" and "This test (female bitterling) will prove of clinical value over the Aschheim-Zondek and the Friedman test." Whatever the explanation they attempt to offer as to the reason for comparing the fish test with the accepted pregnancy tests, it may be mentioned here that the basis of the established pregnancy tests (Aschheim-

\*This work was carried out with the aid of a grant from the Lucius N. Littauer Foundation, Inc.

Zondek and Friedman tests) is the presence of the hormones of the anterior lobe of the pituitary gland or the A.P.L. hormone in the urine of pregnancy in tremendous amounts. The fish have been shown not to react to stimulation by these hormones by many investigators, including Kanter, Bauer, and Klawans themselves. Kanter, Bauer, and Klawans now state: "As was feared it was immediately assumed by many of our readers that we were advocating a new biologic test for pregnancy and because of such misinterpretation the caution that was exercised in avoiding definite conclusions was apparently unavailing." They apparently do not heed their own warning, since in the third page thereafter we read: "In an attempt to evaluate the possibilities of the test upon the bitterling as a pregnancy test, we ran 132 consecutive specimens of urine parallel to the Friedman tests. . . . Table III shows the result of this study. The tests agree in 84.4 per cent of the cases." In their discussion at the end of the paper they state, "The test for estrogenic hormone using the ovipositor lengthening function of the Japanese bitterling\* as the criterion has proved to be of value in detecting excesses of the hormone in the urine of females associated with pregnancy, endocrine disturbances, and chronic cystic mastitis." Again, "In attempting to use this reaction as a test for pregnancy, several precautions are advisedly given. . . . We feel that in conjunction with one of the other biologic tests the test upon the bitterling will prove of value as an aid in diagnosis where ectopic pregnancy, incomplete abortion, missed abortion, placental polyp, or any other condition where the death of the fetus is suspected." It is not to be wondered at that others misinterpret their remarks when they themselves do so. However, they show that 23 normal nonpregnant women out of 40 gave positive bitterling tests. We may thus use Kanter, Bauer, and Klawans' own records to substantiate our first contention that the female bitterling test is *not a test for pregnancy* no matter how well their pregnancy findings agree with the Friedman test.

Kanter, Bauer, and Klawans furthermore claim that "estrogenic substance is fairly firmly established as the exciting factor in the production of the phenomenon that constitutes the criterion for the test." They apparently do not realize that many things are estrogenic in nature, such as many vegetables, coal tar products, and many substances of varied chemical composition which are not hormones.<sup>12, 13</sup> The male hormone derived from the testes, testosterone, which has no relation to a pregnancy test, is an estrogenic substance.<sup>14</sup> Moreover, crystalline androsterone, which is the male hormone found in urine, has given markedly positive fish tests within twenty-four hours, and is not estrogenic in nature.<sup>14</sup>

\*Here we reiterate that the Japanese and the European bitterlings are considered to be identical in ovipositor and ovulatory mechanism by the authorities of the New York Aquarium. We suggest the simple term "Female Bitterling Test" so as not to confuse this test with a male bitterling coloration test.

Their explanation of the bitterling test is evidently untenable. It is the one first put forth by Fleischmann and Kann and recently disproved by Ehrhardt and Kühn. The latter showed<sup>5</sup> that Kanter, Bauer, and Klawans were mistaken in considering this test as a test for estrogenic hormone. They obtained unsatisfactory results with the bitterlings, using urines from pregnant mares which are known to contain tremendous amounts of estrogenic substances, and which is the commercial source of many of our common therapeutic hormone preparations.

The histologic and anatomical remarks of Kanter, Bauer, and Klawans also deserve some notice. They maintain, "The ovipositor has the histology of the human cervix uteri. Under stimulation there is a dilatation of the lumen, the blood vessels, and the lymphatic spaces, with occasional pigmentation but no actual cellular changes. The ovary and oviduct are unaffected by the artificial stimulants. If we may be allowed to draw analogies between the fish and the mammals, we see the same thing in the mouse, the rat, and the rabbit under estrogenic hormone stimulation, changes in the cervix and vagina with no noticeable effect upon the ovaries." However, Fleischmann and Kann<sup>15</sup> studied the histology of the ovipositor some few years ago and found no resemblance to any pelvic organ of the mammal. They described the ovipositor as a thin tube the cellular structure of which resembles no part of the genital system in mammals. They maintained that it is regarded as a modification of the outer skin and is composed of an outer epidermis and cutis, and an inner thin lining of epithelial cells. It is generally accepted by ichthyologists\* that the ovipositor is merely an external egg-laying tube of epidermal tissue and has no relation at all to the oviducts or the cervix uteri. Further, in the same paragraph Kanter, Bauer, and Klawans state that the ovaries and oviducts are not affected in the bitterling by the estrogenic substances, and yet it is well known that the oviducts are greatly affected in mammals upon being stimulated by estrogenic substances.

The results which Kanter, Bauer, and Klawans tabulate of various estrogenic hormone preparations and other glandular substances are interesting from several standpoints. We can corroborate many of their results which we had independently made. Thus, we obtained positive results in forty-eight hours with the bitterlings using doses of 45 and 135 R.U. of progynon tablets, 50 R.U. of aqueous commercial theelin and 200 R.U. of theelin in oil and irregular results with emmenin.† We also obtained negative results with antuitrin-S and A.P.L. Like Kanter, Bauer, and Klawans we obtained negative results in forty-eight hours with the pure crystalline female hormones, theelin and theelol. As is

\*We are grateful to Mr. Christopher W. Coates of the New York Aquarium for this explanation and for his kind cooperation.

†We wish to acknowledge the generous supply of Progynon, Androsterone and Testosterone from Schering Corp., Bloomfield, N. J., and the Emmenin and A.P.L. from Ayerst, McKenna & Harrison, Rouses Point, N. Y.



well known, these are estrogenic and in explanation of their inactivity they suggest that "in the crystallization process, changes take place in the estrogenic products that decrease the efficiency of their action upon the ovipositor of the bitterling." It is surprising that over 2,000 R.U. of estrin require two weeks to produce a positive fish test while relatively few capon units of the *crystalline* male hormones, androsterone or testosterone, give a positive fish test in forty-eight hours. Furthermore, the reliability of any reaction which is noted after ninety-six hours is very doubtful, inasmuch as regression of even exceptionally long ovipositors usually begins before that time. We must therefore disregard all of Kanter, Bauer, and Klawans' positive reactions which are recorded after ninety-six hours.

Kanter, Bauer, and Klawans also mention a personal communication from Norris J. Heckel who "has found that normal adult male urine gives positive tests using the technic that we have described but if the amount of urine is decreased the tests become negative." This corroborates our findings with male urine as reviewed below.

#### EVIDENCE FOR THE USE OF THE FEMALE BITTERLING AS A TEST FOR MALE HORMONE

In April, 1935, it was shown that the work of Kanter, Bauer, and Klawans was not correct so far as the diagnosis of pregnancy was concerned.<sup>9</sup> We then continued the investigation to find out exactly what was the responsible factor in this fish test. On Jan. 29, 1936,<sup>6</sup> we showed that the fraction of extracted male urine which produced the fish test also produced the capon test, and the fraction which contained the female hormone produced no ovipositor change and no capon change. Both crude female and male fractions of normal male urine were estrogenic in nature.

Similarly, the urines of pregnancy were extracted for the male and female hormones and the male fraction was the only one to give the fish test. We are of the opinion that positive reactions caused by all the commercial products are due to male hormone contaminations. We have also tested other substances which are closely related to the male hormones and containing the cholane nucleus, namely, theelin, theelol, ergosterol, cholesterol, and sodium taurocholate,<sup>16</sup> on the fish and no positive reactions were obtained. Slight effects were sometimes obtained with tremendous doses. To confirm the experiments with male hormone, synthetic crystalline androsterone and testosterone in very small amounts (0.6 to 1.2 mg.) gave positive results on the fish in forty-eight to seventy-two hours.<sup>7</sup> To explain why male hormone is the causative factor is not a very simple thing; however, we believe that the male in its spawning season excretes its hormone in the vicinity of the female, and she is thereby stimulated to lengthen the ovipositor and thus deposit her eggs in a mussel. In support of this idea, which we realize is only an hypoth-

esis, neither we nor Kanter, Bauer, and Klawans have observed any spontaneous lengthening of a single ovipositor during the breeding season when the females were kept segregated from the males.

Realizing the unreliability of the fish test as a test for pregnancy, we have performed quantitative male hormone determinations on some thirty medical students who are normal male adults. We used twenty-four-hour urines only and were careful in the collection and the manner of obtaining the total daily outputs, so that we were able to determine with some degree of accuracy the amounts of male hormone excreted daily by normal males. The average amount of male hormone excreted was 30 to 40 bitterling units per day, while the normal variations were from 15 to 95 B.U. excreted per day.

The use of casual specimens as in the technic of Kanter, Bauer, and Klawans is not reliable from a quantitative standpoint. We have noted a positive and a negative result in two successive samples of urine from

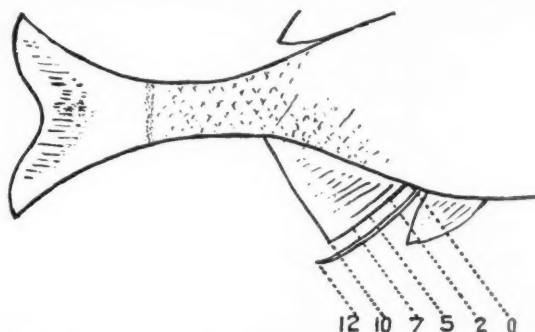


Fig. 1.—Scale used in measuring the length of the ovipositor of the female bitterling.

We tentatively define a bitterling unit as the amount of material which when added to a tank containing two female bitterlings in 4 liters of water, produces an increase in growth of 7 or more on our scale in one of the two fish. The scale used is as follows: an ovipositor which is not visible is 0; if equal in length to that of the anal fin the reading is 10; if half the anal fin, 5, etc. (i.e., ten times the ratio of the length of the ovipositor to that of the anal fin) (Fig. 1).

the same patient taken at hourly intervals. It must also be observed that many urines are toxic to the fish. However, the simple expedient of dialysis of the urine against running water renders all urines non-toxic.<sup>17</sup>

Further quantitative work will be done as soon as the fish's spawning season is over, since we have noticed each year conflicting results occurring during tests made in the breeding season. Pathologic cases will be of especial interest with particular reference to therapy in dysfunctions of the endocrine system.

#### SUMMARY

It is shown that the lengthening of the ovipositor of the female bitterling by external stimuli cannot be considered to be a test for estrogenic hormones *per se*. There are substances excreted in most normal urines

which initiate this phenomenon. We have shown that these causative agents are the male hormones and have established in a preliminary way the daily amounts excreted by normal male adults.

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## EFFECT OF MOCCASIN SNAKE VENOM (ANCISTRODON PISCIVORUS) ON PARTURIENT AND PUERPERAL BLEEDING

EDWARD J. DAVIN, M.D., FRANK SPIELMAN, M.D., AND  
JAMES ALAN ROSEN, M.D., NEW YORK, N. Y.

(From the Gynecological and Obstetrical Service of the Lincoln Hospital)

FOLLOWING the observation by Peck and Sobotka<sup>1</sup> that animals could be made refractory to the Schwartzman phenomenon<sup>2</sup> by injection of moccasin snake venom, Peck deduced that this effect was due either to some change in the blood vessel walls or to some effect upon the clotting factors of the blood. Upon this basis in 1932, he<sup>3</sup> treated various hemorrhagic conditions in human beings with snake venom and obtained marked improvement in the conditions. Since that time Peck and Goldberger<sup>4</sup> have shown the value of the treatment in functional uterine bleeding, Greenwald<sup>5</sup> in thrombocytopenic purpura, and Dack<sup>6</sup> and Goldman<sup>7</sup> in excessive nasal hemorrhages. In their last two reports Peck and his coworkers<sup>8, 9</sup> have correlated the results obtained in different types of bleeding, leaving little doubt as to the efficacy of this method of therapy.

On the strength of the work already done the use of snake venom suggested itself in obstetric bleedings, and accordingly investigations were undertaken to determine the effects produced by the material on the blood lost at parturition and during the puerperium.

## PROCEDURE

Five groups of normal obstetric cases were chosen. In order to determine the normal total period of bleeding during the puerperium, observations on a group of 50 cases were made daily and the length of time that bloody lochia persisted was recorded. This group was used as a control. A second group, consisting of 51 cases was then given snake venom injections and the same observations as to the persistence of puerperal bleeding made. The criterion used for the determination of cessation of bleeding was complete absence of discoloration of the lochia.

A third group of cases, 20 in number, were studied for normal blood loss at parturition, and here only cases of spontaneous, normal delivery without anesthesia or analgesia were observed. This group also served as a control, for comparison with a fourth group of 9 patients who were given snake venom constantly for from two to four weeks prepartum, and postpartum as well. The blood lost during delivery was carefully measured in both groups and the simplest method of collection was employed. This consisted in catching every drop of blood in varying-sized basins, and saving all sponges, pads, drapes, etc., used, from which the blood was subsequently squeezed out. The totals thus obtained were measured and recorded. This method was uniformly employed in all cases included in these two groups.

The injections of the venom were administered subcutaneously three times weekly to once daily and the dosage varied from 0.2 to 2 c.c., of a 1:3,000 solution in saline. In the early cases the initial dosage was 0.2 c.c., but due to the tendency toward localized skin reactions at the site of injections with this dose, the initial quantity given was changed to 0.5 c.c. Reactions in this way were almost completely eliminated. Injections of venom were given either until bleeding had completely disappeared, as in the postpartum cases, or until parturition occurred, as in the prepartum cases.

In order further to check the results obtained, a fifth group consisting of 13 patients were given ergoklonin by mouth, one teaspoonful 3 times daily for ten days following delivery. The effects of the ergoklonin as compared to the snake venom could then be evaluated.

In addition to the above studies, cord bloods from the newborn of those patients injected prepartum were collected at the time of delivery and turned over to Dr. Peck\* for determination of the presence or absence of antivenins. This was for the purpose of showing whether or not the venom injected into the mother actually entered the fetal circulation.

## RESULTS

The results can readily be seen by reference to the charts. The duration of puerperal bleeding in normal cases (Table I) was found to be much longer than is commonly believed, the actual period varying from nineteen to forty-nine days. Comparison of these cases with those which received venom during the puerperium shows the marked difference in the injected group. Here the duration of bleeding varied between seven and nineteen days. The fact that such large series of cases were observed with such uniform results should be sufficient for critical analysis.

The normal blood loss at delivery (Table II) varied from 155 c.c. to 340 c.c. Although the method used in these determinations was rela-

\*The authors wish to express their appreciation to Dr. Peck for the supply of the snake venom used in this work as well as many helpful suggestions. The venom is now available commercially and is manufactured by Lederle & Co.

tively crude, this factor is of no great importance in judging results since it was employed on all observations. The differences between the blood loss during parturition of noninjected cases as compared to those injected, is strikingly brought out by reference to Table III. In 7 of the 9 cases the blood loss was only from 15 to 100 c.e., 1 case lost 255 c.e., and 1, 500 c.e. In the latter, difficult midforceps delivery was followed by uterine atony. It is interesting to note that puerperal bleeding following puerperal administration of venom in large doses, 2 c.e. daily, was reduced to from five to eight days. Undoubtedly this dosage played an important rôle.

TABLE I  
COMPARISON BETWEEN INJECTED AND CONTROL GROUPS OF CASES

	NO. OF CASES	NO. OF VENOM INJECTIONS	DURATION OF PUERPERAL BLEEDING (DAYS)
Controls	50	None	19 to 49
Injected cases	51	5 to 12	7 to 19

TABLE II  
NORMAL BLOOD LOSS AT DELIVERY—CONTROLS. ALL CASES DELIVERED SPONTANEOUSLY WITHOUT ANESTHESIA

PATIENT	AGE	PARITY	LENGTH OF LABOR	BLOOD LOSS
1. J. D.	43	3	6 hr.	340 c.e.
2. C. C.	23	2	15 hr.	220 c.e.
3. I. M.	24	2	8 hr.	200 c.e.
4. G. M.	19	1	18 hr.	270 c.e.
5. A. D.	22	1	17 hr.	200 c.e.
6. A. O.	28	3	11 hr.	250 c.e.
7. V. E.	26	2	11 hr.	300 c.e.
8. E. W.	30	3	8 hr.	180 c.e.
9. L. R.	20	3	3 hr.	190 c.e.
10. C. M.	29	3	8 hr.	180 c.e.
11. M. B.	30	2	12 hr.	265 c.e.
12. E. Z.	23	2	10 hr.	165 c.e.
13. M. H.	26	3	5 hr.	205 c.e.
14. K. P.	30	4	7 hr.	155 c.e.
15. E. W.	27	1	9 hr.	295 c.e.
16. H. B.	22	2	19 hr.	265 c.e.
17. H. B.	33	3	16 hr.	210 c.e.
18. J. C.	33	1	5 hr.	220 c.e.
19. S. M.	27	1	4 hr.	180 c.e.
20. G. P.	23	1	15 hr.	215 c.e.

Table IV shows the effect of ergoklonin administered to a group of 13 cases. All but one were bleeding at the time of discharge from the hospital on the tenth day postpartum.

The examination of the cord blood by Dr. Peek of patients injected before delivery failed to show the presence of antivenins, leading to the conclusion that the venom did not enter the fetal circulation.

It is to be stressed that at no time were any serious untoward effects observed which could be attributed to the administration of the snake



TABLE III  
CASES TREATED WITH VENOM BOTH ANTE- AND POSTPARTUM

PA- TIENT	AGE	PAR- ITY	DOSAGE OF VENOM INJECTIONS GIVEN ANTEPARTUM											BLOOD LOSS AT DELIVERY	DOSAGE OF VENOM INJECTIONS GIVEN POSTPARTUM					PERIOD OF POST- PARTUM BLEEDING		
			0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	2.0		2.0	2.0	2.0	2.0	2.0		2.0	2.0
E. P.	27	3	0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	255 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	6 days
A. F.	23	2	0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	15 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	6 days
T. T.	26	2	0.5	0.8	1.0	1.5	1.5	1.5	2.0	2.0	2.0	2.0	c.c.	80 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	6 days
B. K.	26	2	0.5	0.8	1.0	1.5	2.0	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	100 c.c.	1.5	1.5	1.5	2.0	2.0	2.0	c.c.	8 days
C. F.	27	1	0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	80 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	5 days
R. P.	18	3	0.5	0.8	1.0	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	c.c.	60 c.c.	1.5	2.0	2.0	2.0	2.0	2.0	c.c.	7 days
E. P.*	19	1	0.5	0.8	1.0	1.5	1.5	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	500 c.c.	1.5	1.5	1.5	2.0	2.0	2.0	c.c.	8 days
M. H.	33	1	0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	100 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	7 days
J. C.	21	2	0.5	0.8	1.0	1.5	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	50 c.c.	2.0	2.0	2.0	2.0	2.0	2.0	c.c.	6 days

\*Midforceps, difficult delivery followed by uterine atony.

venom. Localized skin reactions at the site of injections consisting of erythema and edema were occasionally noted in the early cases where small initial doses (0.2 c.c.) were employed, but these reactions quickly disappeared under simple treatment, and did not recur with subsequent injections. Peck and Rosenthal<sup>8</sup> mention the not infrequent need for desensitization of patients, but in the series here presented this procedure was never necessary.

TABLE IV  
EFFECT OF ERGOKLONIN UPON POSTPARTUM BLEEDING

PATIENT	AGE	PARITY	ERGOKLONIN ADMINISTRATION	LOCHIA DURING FIRST TEN DAYS POST-PARTUM
M. M.	23	2	Drams 1 three times daily	Bloody
R. K.	19	2	Drams 1 three times daily	Bloody
E. D.	30	2	Drams 1 three times daily	Bloody
A. S.	24	2	Drams 1 three times daily	Bloody
F. S.	25	1	Drams 1 three times daily	Bloody
H. O.	28	1	Drams 1 three times daily	Clear on ninth day
J. K.	27	2	Drams 1 three times daily	Bloody
A. W.	24	1	Drams 1 three times daily	Bloody
H. M.	28	4	Drams 1 three times daily	Bloody
C. M.	21	3	Drams 1 three times daily	Bloody
A. J.	26	3	Drams 1 three times daily	Bloody
J. G.	27	1	Drams 1 three times daily	Bloody
J. S.	35	3	Drams 1 three times daily	Bloody

#### COMMENT

Careful study of the tables presented shows such striking results that little comment is necessary. This is especially true of the controls and cases injected shown in Table I. Here the large series of cases leave little room for skepticism, and emphasize the efficacy of snake venom administration. Table III is extremely interesting because larger doses (2 c.c.) were used over long periods of time and the effects of both pre- and postpartum venom injections could be observed. Table IV, showing the results of ergoklonin given for 10 days after delivery, only serves to emphasize the effects produced by the venom.

From a practical point of view considerable work remains to be done before recommendations that snake venom be universally employed for the control of bleeding in obstetrics can be made. Since the exact modus operandi of this material is still unknown, the more familiar pituitrin and ergot must still represent the drugs of choice in the normal case. However, in cases of severe anemia where it is advisable to cut the blood loss at parturition and in the puerperium to a minimum, snake venom may prove extremely valuable, especially where there is a history of excessive bleeding during previous deliveries. It should also be given a trial purely empirically in postpartum hemorrhages, even though its effect may be delayed.

The fact that it does not produce deleterious effects in either mother or child is of great importance, since the hemorrhagic conditions hereto-

fore treated by venom may also be treated in the presence of pregnancy.

As is evident, further investigations are necessary before far-reaching conclusions can be drawn. The most important, it appears to the authors, is the determination of the mechanism by which the snake venom effects are produced.

#### SUMMARY AND CONCLUSIONS

1. The period of puerperal bleeding in a group of 51 cases receiving snake venom injections postpartum was materially shortened as compared to the duration of bleeding in a group of 50 controls.

2. The blood loss during parturition in a group of 9 cases which received antepartum injections of venom was distinctly decreased in comparison to a group of 20 controls. Postpartum administration of the material also lessened the period of puerperal bleeding in these cases.

3. Puerperal bleeding was present in all but one of the 13 patients treated puerperally with ergoklonin for at least ten days after delivery.

4. The inability to demonstrate the presence of antivenins in cord bloods obtained at delivery after prepartum injections of venom indicates that the material does not enter the fetal circulation.

5. No deleterious effects that could be attributed to the snake venom upon either mother or child were observed.

6. The use of this material is recommended in the severe anemias as well as other bleeding conditions associated with pregnancy, and especially where a previous history of excessive hemorrhages in previous pregnancies is obtained.

7. Although the results obtained up to the present are very encouraging, considerable work remains to be done before the material can be recommended for every obstetrical case. In the authors' opinion, the most important problem is the determination of the *modus operandi* of snake venom effects in the human being.

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313 W. 103RD STREET

145 W. 86TH STREET

## ADDITIONAL DATA ON THE TREATMENT OF UTERINE BLEEDING WITH SNAKE VENOM\*

MORRIS A. GOLDBERGER, M.D., AND SAMUEL M. PECK, M.D.,  
NEW YORK, N. Y.

(From the Gynecological Service of the Mount Sinai Hospital)

IN A previous report the therapeutic effects of mocassin venom (*Anistrodon piscivorus*) in twelve cases of functional uterine bleeding were presented.<sup>1</sup> The clinical results obtained warranted further trial in cases of this kind. The present report embodies subsequent observations on some of the cases already reported, with the addition of new cases.

### METHOD OF ADMINISTRATION

The mocassin venom was used in a 1:3,000 dilution with sterile sodium chloride (normal) containing 1:10,000 merthiolate. The venom was obtained through the courtesy of Dr. Raymond L. Ditmars of the New York Zoological Gardens.† The dosage and the method of administration have been modified.

All injections were given subcutaneously. The initial injection was 0.5 c.c. and subsequent injections were rapidly increased to 1 c.c. (by the third injection). The interval between administrations of the venom depended on the severity of the bleeding. It was advisable to give as much venom as possible the first ten days, because at about that time the majority of patients developed a sensitivity to the venom which necessitated a decrease in the amount until desensitization was accomplished.

There was a distinct quantitative relationship between the desired clinical effect and the amount of venom given. In cases with marked bleeding, 1 c.c. of the 1:3,000 dilution was given daily or even twice a day until the hemorrhage was controlled. In a number of the patients, daily injections were given at the beginning of the treatment. After the bleeding had been controlled the interval between injections of venom was increased so that only two or three treatments were given weekly.

If the subsequent menstrual period approximated the normal, two injections a week were administered for at least three normal menstrual periods. During the course of the treatment a maintenance dose had to be established.

In a number of the treated individuals a period of from six months to one year of normal menstruation occurred after the venom therapy had been discontinued. When metrorrhagia or menorrhagia recurred and venom was again administered, the initial dose was 1 c.c. If such a patient reported for treatment early enough, several 1 c.c. injections given two or three times weekly were found to be sufficient to bring about normal menstrual bleeding. It has also been noted that the course of injections necessary to control recurrences of bleeding was shorter than that necessary at the beginning of the treatment.

### HYPERSENSITIVITY REACTIONS

In some cases a hypersensitivity to the snake venom protein occurred about the tenth day. This was characterized by an egg-shaped

\*For lack of space detailed tabulations are omitted but may be found in the authors' reprints.

†Venom for clinical use can be obtained from the Lederle Laboratories.

erythematous swelling at the injection site which appeared after eight to twelve hours. No general reaction was ever observed. Desensitization could easily be brought about by reducing the subsequent injections to 0.05 to 0.1 c.c. of the 1:3,000 dilution and gradually increasing to the 1 c.c. dose. In marked cases of hypersensitivity, the following series of injections may be given: 0.1 c.c. of 1:10,000; 0.4 c.c. of 1:10,000; 0.2 c.c. of 1:6,000; 0.4 c.c. of 1:6,000; 0.1 c.c. of 1:3,000; and 0.4 c.c. of 1:3,000. In the majority of cases the first suggested method was followed as it saved considerable time and was well tolerated.

It is important that therapeutically active venom be used. Previous reports have shown that the venom of individual moccasin snakes varies markedly in its content of the factor or factors responsible for the therapeutic effect.<sup>2</sup> At present, pooled venoms which are titrated on patients are used. It is necessary to bear in mind that venom solutions more than a year old should not be used.

#### MECHANISM OF ACTION OF VENOM

Previous clinical and laboratory experiments have clearly shown that circulating substances were not the cause of the antihemorrhagic effect produced by moccasin venom injections.<sup>3</sup> The reversal of the positive venom test in purpura after treatment and the reduction in the size of the vessels in cases of hereditary familial telangiectasis as well as histologic studies seem to show that the venom has a direct effect on small blood vessels, making them more resistant to bleeding.<sup>4, 5</sup>

Twenty cases of functional uterine bleeding treated with injections of moccasin snake venom are reported. Similar treatment was administered to five cases of uterine bleeding due to fibromyomas.

#### SUMMARY

Satisfactory clinical results were obtained in seventeen of the twenty functional uterine bleeding cases treated with the moccasin snake venom. The period of observation of these cases varied from two months to four years. Poor results were obtained in three cases. These are reviewed:

CASE 1.—Continuous bleeding was controlled. There was a decrease in the amount of hemorrhage and an increase in the free interval. However, this case was considered to be a poor result because the patient continued to have periods at two- to three-week intervals. The dosage in this case was inadequate.

CASE 2.—The period of treatment and observation was too short to warrant conclusions. This patient failed to return for further treatment.

CASE 3.—The treatment of this patient extended over a period of four years. A summary of her history is as follows:

A twenty-year-old girl whose menstruation began at eleven years of age. It occurred regularly every month for one week up to the age of thirteen, when severe



and alarming menometrorrhagia began. In the past seven years she has had six hospital admissions. Her treatments included (1) dilatation and curettage (hyperplastic endometrium and cystic degeneration were found); (2) parathormone, pituitrin, thyroid, insulin injections; (3) x-rays to spleen and pituitary; (4) in 1928 castration dose of x-rays to ovaries with moderate relief and then an exacerbation of the bleeding; (5) she was admitted to the hospital in July, 1934, with a hemoglobin of 35 per cent, and a transfusion was given.

*Physical Examination.*—Pallor; pulse, 92; blood pressure, 120/64; blood chemistry, basal metabolic rate and sugar tolerance test are all normal; Wassermann test, negative; thyroid, isthmus palpable; marked precordial thrill (felt in the fourth interspace to left of sternum); heart enlarged to left; harsh systolic murmur over precordium; spleen not palpable; gynecologic examination, negative.

*Course Under Venom Therapy (Chart 1).*—A graph of the menstrual bleeding during venom treatment shows that from January, 1932 to June, 1932 she had regular, normal periods. This regularity continued up to May, 1933, although

GRAPH of UTERINE BLEEDING BEFORE and DURING TREATMENT  
CASE 8

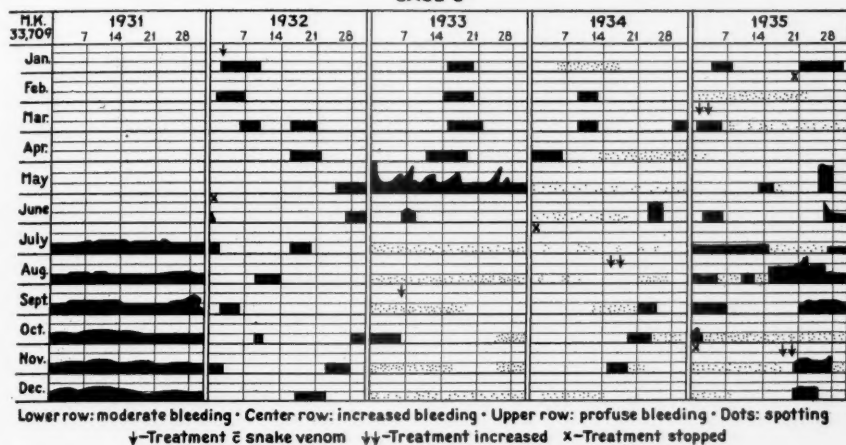


Chart 1.—A typical case of functional uterine bleeding treated with moccasin venom.

treatment had been stopped. In May, 1933, she had moderate to profuse bleeding for an entire month. In June she had a short period and then had continuous spotting in July and August, 1933. In September, treatment was resumed. The dose of venom was 1 c.c. three times a week, but this dose was insufficient as she continued to spot with varying free intervals. The dose was increased and in October, November, December, 1933 and January, 1934, the menstrual periods were normal. In April, May, and June, 1934 there was irregular spotting with a three-day moderate period in June. Treatment was not given in July as patient was on her vacation. In the middle of August, 1934, treatment was resumed and there were regular periods in September, October, and November. In December she spotted thirteen days. In January, 1935, she had two periods. In February there was irregular spotting and the patient was hospitalized for cardiac insufficiency. On discharge from the hospital, venom therapy was again administered and seemed to control her bleeding until the latter part of June when her periods became more irregular and profuse. The dose was then increased to 2 c.c. of the 1:3,000 dilution given four times a week and then further increased to 1 c.c. of 1:1,000 three times a week before bleeding was controlled.

This patient presented a complicated problem. She was a congenital cardiac, undernourished, anemic, and in extreme poverty. She had been treated by castration doses of x-rays to the ovaries and x-ray therapy to the pituitary and spleen and continued to have severe uterine bleeding. The venom treatment was used in the last four years. The result with this treatment during the last year and a half has been poor, yet we feel that without treatment she would have had increased uterine bleeding. This case demonstrated the effect of venom therapy administered over a prolonged period. Although the patient received relatively large doses of venom no toxic effects were manifest.\*

#### UTERINE BLEEDING DUE TO FIBROIDS

Snake venom was also used experimentally in five cases of uterine bleeding due to fibroids. It was felt that in these cases venom had very little effect, especially if the fibroids were submucous. In several instances, although the bleeding was controlled at first, the venom became ineffectual with the increase in size of the fibroids.

#### CONCLUSIONS

1. Moccasin snake venom injections have been used with good results in seventeen of twenty cases of functional uterine bleeding.
2. The control of bleeding probably results by means of the action of the venom on the uterine capillaries, making these vessels more resistant to hemorrhage.
3. The method of treatment is offered as a procedure which will control functional uterine bleeding until there is a return to normal menstruation.
4. Adequate dosage based on clinical symptoms must be determined for each patient.
5. Moccasin snake venom has very little effect on uterine bleeding due to fibromyomas.

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\*A polyp, 1½ by ½ inch, protruding from the cervix, was removed on September 2, 1936.

## CHORIONEPITHELIOMA WITH ESPECIAL REFERENCE TO ITS RELATIVE FREQUENCY

EDWARD A. SCHUMANN, A.B., M.D., F.A.C.S., AND  
ADRIAN W. VOEGELIN, M.D., PHILADELPHIA, PA.

**C**HORIONEPITHELIOMA may well be termed a tumor of vagaries, both because of its often unpredictable degree of malignancy and because of the great variation in its incidence.

A third peculiarity of this neoplasm is the practical difficulty of reaching an accurate diagnosis from curettings, a number of tragic errors having resulted from this fact.

Since the development of the biologic tests for pregnancy, chorionepithelioma may generally be diagnosed by the persistence of a positive urinary reaction after abortion, labor or mole pregnancy, and especially if the test be positive with greatly diluted urine. However, even this diagnostic factor may fail, as will be shown in the history of the case here reported.

The incidence of chorionepithelioma is uncertain, many widely differing estimates having been made. In eighteen months' time, 7 cases were found among 2,700 autopsies in Vienna, while in Budapest not one case was found during a search extending over several years. Symmers states that in 12,000 autopsies performed at Bellevue Hospital, he did not encounter a single specimen of chorionepithelioma, and that in the fourteen years following the establishment of the pathologic laboratories in Bellevue, only one such tumor was discovered, this being a metastatic growth in the vagina.

To determine the incidence in one large city, we followed the plan of circularizing all the hospitals within the corporate limits of Philadelphia. It was thought that every case of chorionepithelioma developing in the city would sooner or later come to hospitalization, so that a fairly accurate census of all cases might be obtained. If these cases were checked against the total number of births reported to the Bureau of Vital Statistics during the same interval, the ratio of chorionepithelioma to pregnancy could be fairly well established.

This calculation made no provision for unreported abortions, and since it is commonly believed that one abortion to four full-term pregnancies is a reasonably correct proportion, 25 per cent of the number of births were added to them to obtain the total number of pregnancies.

The years 1929 to 1933 inclusive were studied, and so far as possible the subsequent life histories of the patients suffering from chorionepithelioma were followed.

In this five-year period there were 166,166 births reported to the Bureau of Vital Statistics. If to them be added 25 per cent to account for abortions, or 41,541, the total pregnancies in Philadelphia in the five years studied would have been 207,707.

Inquiry from the city's hospitals disclosed the fact that during the same interval fifteen cases of known chorionepithelioma had been admitted. The diagnosis in these cases had been made either from the extirpated uterus or curettings plus biologic tests.

The ratio of chorionepithelioma to pregnancy in Philadelphia during a five-year period was as one to 13,847 pregnancies or, roughly, 1 to 13,850.

Analyzing the fate of the 15 women, 8 died either immediately following operation or within a few months, of metastasis. Two were lost to sight and 5 remain well.

The immediate mortality, then, in the patients whose fate is known, was 53 plus per cent, while the salvage was a little better than 33 plus per cent, the result in the remaining two women being unknown.

In 8 of the 15 patients, the chorionepithelioma was preceded by a mole pregnancy, various times having elapsed between the mole and the chorionepithelioma, in one instance, five years. During the same five-year period 78 hydatidiform moles were found in the records of Philadelphia hospitals. Most patients were treated by hysterectomy, either supravaginal or total, with radium and x-ray postoperative.

The diagnosis was made from curettings in 9 of the 15 cases, and in 10 the Friedman test confirmed the findings. In the earlier cases this test was not routinely performed, but if one ignores these five, it will be seen that biologic estimation of the urine hormones was confirmatory in all but one, a case which presents so many points of interest in the diagnosis and management of this bizarre condition that it is reported in some detail.

#### CASE REPORT

L. G., thirty-three years of age, entered Kensington Hospital for Women, Feb. 28, 1933, complaining of vaginal bleeding, backache, bearing-down sensations. She had been in previous good health; had had two full-term pregnancies and one miscarriage five years before. (The patient failed to inform us, and it was not until after her death that it was learned, that the miscarriage described was really an hydatid mole.) The present illness began two weeks before admission, with an exacerbation of an old backache and irregular vaginal bleeding. There was some suspicion of a very early miscarriage. On examination the general physical condition was good. There was no abnormality in the blood or urine. The cervix was soft, the uterus large and boggy and retroverted to the third degree. A diagnosis of incomplete abortion with retroversion was made, and the patient was operated upon under avertin anesthesia.

The uterus was found subinvolved, retroverted. The appendix presented some evidence of catarrhal inflammation, and curettage revealed a moderate amount of spongy tissue. After appendectomy and Baldy suspension of the uterus, the patient made an uninterrupted recovery.

Microscopic examination of the curettings showed greatly degenerated placental villi which in places contained nests of syncytial cells varying considerably in size and shape (Fig. 1).

This tissue was regarded as somewhat suspicious and, accordingly, a Friedman test was made which was negative. The tissue was then submitted to a tumor conference and a diagnosis of deciduitis was returned.

Two months later the patient reentered the hospital stating that she had been having some slight vaginal bleeding daily since the operation. The pelvic examination was negative and upon curettage a few fragments of tissue were obtained. The laboratory report at this time states that the findings were similar to those of the previous curettings and that no evidence of chorionepithelioma was present. Another Friedman test at this time was negative.

On October 4 the patient reentered the hospital with a history that she had gone to the office of a neighborhood physician for a local treatment and had there



Fig. 1.—Curettings from which a diagnosis of deciduitis was returned. Friedman test was negative.

had a massive hemorrhage. On examination the uterus was found to be markedly enlarged, soft, with a mass of necrotic tissue projecting from the cervix. An attempt at digital removal of this mass resulted in furious hemorrhage, which necessitated an immediate transfusion and abandonment of any attempt at more radical operation.

The tissue obtained presented a typical picture of chorionepithelioma as illustrated in Fig. 2, and at this time the Friedman test was for the first time strongly positive. After two days a rapid vaginal hysterectomy was performed (Fig. 3) with frequent blood transfusions, the patient being in desperate condition, and three weeks after operation the Friedman test was again negative.

The patient was discharged for further observation, rapidly developed cerebral metastasis and died some five months subsequent to operation.

In reviewing this case it is now obvious that the first curettings which were considered to be deciduitis were in reality chorionepithelioma, and



it is important to note that operative procedures were inexcusably delayed by reason of the persistent negative biologic tests.

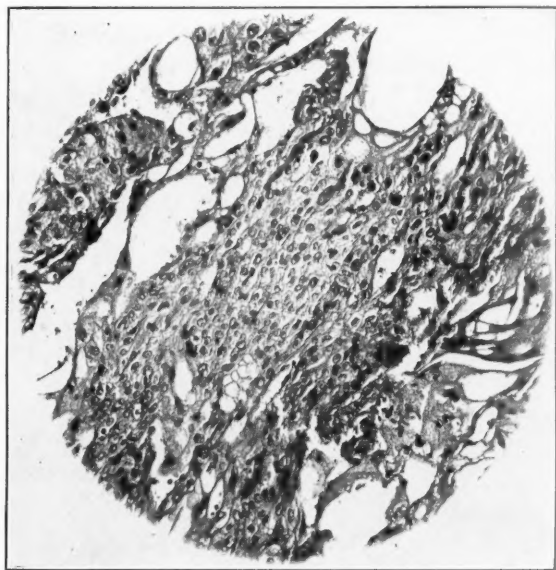


Fig. 2.—Section from the uterine wall at hysterectomy showing typical chorionepithelioma.

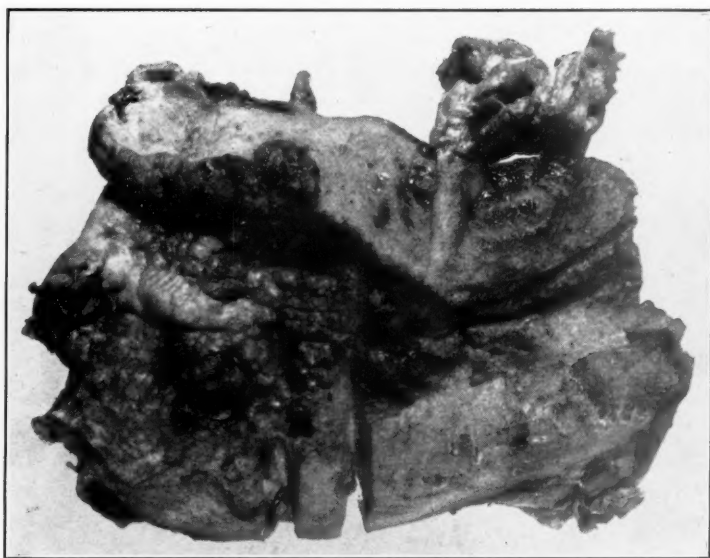


Fig. 3.—The excised uterus filled with neurotic tumor masses.

The careful study of the foregoing case taken in connection with the others in this series demonstrates very clearly that positive Aschheim-Zondek or Friedman tests, especially with high dilution of urine in the

presence of persistent fetal elements in uterine scrapings or tissue masses, render the diagnosis of chorionepithelioma practically certain.

On the other hand, when under the same conditions these tests remain negative, one cannot be sure that a chorionepithelioma of low proliferation and malignant quality is not present. Radical surgery is indicated, therefore, whenever persistent fetal elements are found, especially if irregular bleeding is a symptom, regardless of a negative Aschheim-Zondek test.

## ANALYSIS OF THE FIFTEEN PHILADELPHIA CASES

	MOLE PRE- CEDING	DIAG- NOSIS BY CURET- TING	OPERATION	FRIED- MAN TEST	OUTCOME
1	Yes	Yes	Panhysterectomy	+ after operation -	Well
2	Yes	Yes	Panhysterectomy	+ after operation -	Well
3	No	Biopsy spec.	Radium and total hysterectomy	?	Dead of metastasis 6 months
4	Yes	Yes	None	?	Died
5	No	Yes	None	++	Disappeared from view
6	No	No	On laparotomy found in uterus and ovary	++	Died in one month
7	Yes	No	On laparotomy supravaginal hysterectomy	+	One year later x-ray showed apparent metastasis to kidney. X-ray and radium. Now well
8	Yes	Yes	Supravaginal hysterectomy	+	Died four days after operation
9	Yes	No	Diag. made from extirpated uterus	+	Discharged well; lost to view
10	Yes	No	Diag. made from uterus supravaginal hysterectomy	+	Radium and x-ray Now well
11	No	No	Radium	?	Died of metastases, few months
12	No	No	Diag. made from extirpated uterus	++	Radium death from intra-abdominal hemorrhage
13	Yes	Yes	Vag. hysterectomy	--+	Death from metastases 6 mo. later
14	No	Yes	Hysterectomy	?	Dead of peritonitis
15	No	Yes	Radium	?	Now has vesicovaginal fistula, otherwise well

An interesting question arises as to the type of operation which offers the hope of the best results in these cases.

The commonly accepted plan is to perform an extensive panhysterectomy with removal of both tubes and ovaries.

Since metastasis in chorionepithelioma is generally by way of the blood stream into distant organs, the lungs, brain, and liver being most frequently attacked, whereas secondary growths in the broad ligaments and uterine adnexa are relatively uncommon, it is questionable whether such wide dissection is of any value.

Again, common sites of metastasis are the vagina and vulva, the mechanism of which has not been satisfactorily explained, although von Recklinghausen attempted it in his theory of retrograde lymphatic transmission. These vaginal metastases are peculiar in that they may not make their appearance for months, although sometimes they are noted even before the primary uterine growth has been discovered. Under such conditions, panhysterectomy will be of no avail.

Tumors composed of fetal cells are markedly under the influence of the gonadal hormones, or, rather, seem to exert a profound effect upon the activity and production of these substances. Hence, it would seem advisable to preserve the regularly recurring cycle of estrin and progestin formation in the hope that by this means, retrogression and absorption of the aberrant fetal elements might be facilitated. Allowing the ovaries to remain, therefore, is worthy of trial. Study of the present series of cases has convinced the writers that much more information may be obtained concerning chorionepithelioma; first, by the systematic histologic examination of hydatidiform moles to ascertain whether or not the piling up of decidual cells in portions of certain of these growths taken in conjunction with the subsequent history of the patient is indicative of potential malignancy; and second, by the intensive study of reasonably large groups of cases which may be accomplished by the pooling of material in the larger cities, and its working up by individuals or committees appointed by local obstetric or gynecologic societies.

1814 SPRUCE STREET  
1521 LINDLEY AVENUE

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Settergren, F.: *The Danger of Infection From Catheterization of the Bladder and Indications for Catheterization in Obstetric Cases*, *Acta obst. et gynec. Scandinav.* 16: 202, 1936.

The material comprises 400 cases evenly divided into two groups. In Group 1, each patient was catheterized at least three times before she was discharged from the hospital. No antiseptics were used before the catheter was inserted into the bladder. In Group 2, on the other hand, catheterization was performed only upon definite indications and always under antiseptic precautions. Infections occurred in 29.2 per cent of the first group, and in only 12.2 per cent of the second group. If the presence of pus cells is used as a criterion of infection, the corresponding figures are 20.5 per cent for Group 1, and 5 per cent for Group 2. The author feels certain that the number of urinary infections increased with the number of catheterizations. Only a small number of patients developed subjective symptoms and pyelitis occurred in only one case. Follow-up examinations from two to four weeks after delivery showed spontaneous healing in most instances. The author is of the opinion that urinary antiseptics should be given prophylactically to most women immediately after labor. The author suggests a new way of obtaining sterile specimens of urine after delivery.

J. P. GREENHILL.

## THE CONTROL OF PUERPERAL SEPSIS IN HOSPITAL PRACTICE\*

D. ANTHONY D'ESOP, M.D., NEW YORK, N. Y.

*(From the Sloane Hospital for Women)*

**I**NFECTION of the puerperal uterus constitutes one of the most important complications with which the obstetrician is confronted. The figures on maternal mortality due to sepsis are becoming commonplace knowledge. Even the lay press defiantly waves them before us. This press, poorly guided as it has always been concerning medical subjects, taunts us with the utopian idea that, since puerperal sepsis is a preventable disease, we should make it our job to wipe it out in much the same way as has been done with typhoid fever or diphtheria. Needless to say, the problem with puerperal sepsis is quite different, and for the present, at least, we will have to content ourselves with the fact that a certain amount of sepsis will be inevitable. There is no doubt, however, that the present high incidence of this complication could be materially lowered, and it is toward this end that this plan of control is offered. The various features of the plan have formed the guiding principles of practice at the Sloane Hospital for Women for the past eight years and are largely an embodiment of the ideas along these lines of our director, Dr. Benjamin P. Watson. A general program of control should include not only the measures aimed at the direct prevention of sepsis, but also the management of the patient with the purpose of conserving her resistive forces, so that in the face of an acquired infection she will more effectively combat it.

The subject may be divided under the following headings:

- (1) Control during the antepartum period
- (2) Control during labor
- (3) Control during the puerperium

### CONTROL DURING THE ANTEPARTUM PERIOD

The measures which can be profitably employed during this period are largely designed to build up the resistance of the patient. The patient is given a complete physical examination when she first comes to the clinic. A careful examination will often reveal disease processes complicating the pregnancy, which will require special handling during the antepartum period in order that the body resistance can be maintained at as high a level as possible. A routine estimation of the erythrocyte count and hemoglobin is most important. In our clinic about 9 per

\*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, May 26, 1936.

cent of the patients showed a hemoglobin of 70 per cent or less on admission. Treatment of the anemic patient during this period may be the means of combating infection later on.

Instruction of the patient should stress the importance of a well-balanced diet with emphasis on such food elements as iron, calcium, and the vitamins. Excessive gain in weight should be controlled, since this leads to undue strain which becomes reflected in the patient's general condition at term. An average gain of about 18 pounds is considered ideal. The patient should also be instructed regarding the hygiene of pregnancy. Douching is permitted only under instruction. Coitus is not permissible during the last few months. The importance of coitus as a means of introducing virulent organisms into the vagina just before the onset of labor cannot be accurately determined, but our attention has been called to several cases in which this may well have been the etiologic mechanism. In addition to such instructions as outlined above, the patient should be given a list of reportable symptoms among which should be included the rupture of the membranes. In any case history study of puerperal sepsis there will be found a group that started as antepartum infections of the amniotic sac. Characteristically, these patients, when entering the hospital early in labor, give a history of having ruptured the membranes three or four days before, although they did not think it important enough to report. An examination may reveal the escape of a small amount of amniotic fluid which, as the infection progresses, may become purulent in character. Labor is most often characterized by poor contractions, and by the time the patient is delivered, or shortly thereafter, there is a sharp rise of temperature which may be preceded by a chill. Fortunately, in most instances, the temperature subsides as soon as the uterus obtains its natural drainage following delivery, and the patient gets better, but there are others who develop a spreading sepsis which may end fatally. During the past eight years we have seen three such fatalities.

#### CONTROL DURING LABOR

The first point under this heading deals with the routine nose and throat cultures of the labor room staff. All new students and nurses, as well as the doctors, are cultured for the hemolytic streptococcus. Carriers are excluded from duty until repeated cultures prove negative. The nurses' duties are confined entirely to the obstetric division of the hospital during the period of training, thus avoiding contact with the cases in the medical and surgical wards.

The second point refers to the routine vaginal cultures of the patients for the same organism. During the past three years in the course of several thousand such cultures, we have noted an incidence of 3.4 per cent positives. These patients are isolated as will be described later on. Although they do not seem to show a much higher incidence of infec-



tion than the noncarriers, the morbidity rates of the two groups being 12.2 per cent for the carriers and 7.8 per cent for the noncarriers, we isolate them because we feel that the organisms they carry may be virulent for their neighbors. Until the technic of Lancefield or Hare, by which streptococci can be classified, is applicable to routine clinical work, carriers among the staff and patients will have to be considered potential sources of infection.

The third point concerns the reduction of contacts in the labor room. About three years ago we adopted a contact sheet on which each person who made any physical contact with the patient in labor had to write his or her name. The purpose of keeping such a list was to enable us to make a search for a possible carrier among these contacts when a patient developed an infection. When we started the contact sheet, we were much surprised to find that some patients were handled in one way or another by as many as twenty-five different people. Needless to say, this number has been considerably reduced. It seems only natural to believe that the reduction of such contacts lessens the possibilities for exogenous infections.

The fourth point deals with asepsis. The routine consists of a change from street or hospital clothes and shoes to operating room wear. A cap and a 4-ply gauze mask placed over the nose and mouth complete the dress. We emphatically stress the importance of placing the mask over both the nose and mouth. This is followed by a five-minute scrub of the hands and arms with green soap in running water, alcohol rinse, and sterile long-sleeved gown and gloves. The patient is then prepared with half-strength tincture of iodine. The prepared field includes the vulvar inner aspects of thighs, the suprapubic area and, last, the anal region. The field is then draped with sterile towels, sheets, and leggings. Before the examining fingers are introduced into the vagina, the labia are carefully separated and the vaginal orifice is swabbed with several pledgets of cotton that have been soaked in a 1 per cent lysol solution. The fingers are then introduced directly into the vagina without touching the vulvar skin surfaces. By carrying out the examination in this way, there is little possibility of introducing organisms from the outside into the vaginal canal. We are not much concerned with the particular virtues of the various antiseptics used to prepare the sterile field. It is quite probable that soap and water would do just as well. It is noteworthy that a particular clinic will often change the type of antiseptic after a series of infections have occurred. In addition to this change, various other modifications are made in the technic which, consequently, make everyone infection conscious and result in greater vigilance and care in carrying out the details of the plan. Then, strange as it may seem, when the morbidity rates are studied, all the credit for the more recent lower rate is given to the new antiseptic. Too much empha-

sis on the type of antiseptic used to prepare the skin is not desirable, because it detracts from the importance of other more important features of the technic.

The fifth point deals with vaginal examinations during labor. We believe that a vaginal examination carries no greater risk of infection than a rectal examination, if it is carefully done. The doctor prepares himself and the patient in exactly the same way as he does for the delivery, including the change to operating room clothes and shoes, cap, mask, sterile gown, and gloves. The only exception we make is that for the vaginal examination the sterile field is made smaller. The examining fingers are introduced directly into the vagina without making contact with the vulvar surfaces. If the technic of the vaginal examination is not as good as that employed for the actual delivery, then it is obvious that the technic of the delivery becomes as bad as that used for the vaginal examination.

The sixth point refers to the technical skill and the judgment used in carrying out obstetric procedures. In this category we feel that the following are very important considerations:

1. Make an early appraisal of the prognosis of labor in order to avoid the dangers of the late cesarean section. In spite of all the recent refinements of surgical technic, the late cesarean section carries a high maternal mortality from sepsis. The low flap operation has given us better results than the classical operation so far as infection is concerned, but neither this nor the Latzko type of extraperitoneal cesarean section is a safe procedure in the face of uterine infection.

2. Carry out obstetric operations on defensible indications in order to avoid unnecessary and untimely instrumentation and subsequent trauma. Traumatized tissue has a lowered resistance and therefore favors the activation, invasion and final spread of organisms already present in the vagina, leading to an endogenous type of infection, usually by anaerobic bacteria.

3. Handle the third stage with great care in order to avoid hemorrhage. Excessive loss of blood breaks down the defense mechanism, the only means of cure at the patient's disposal.

4. Repair all lacerations properly.

#### CONTROL OF SEPSIS IN THE PUERPERIUM

This phase of the problem is concerned with two main points: (1) Nursing care in the puerperium. (2) The isolation of infected or potentially infected patients.

With respect to the nursing technic the following are the main points upon which it is based:

1. The nurse masks the nose and mouth before she does a perineal dressing.
2. She scrubs her hands and arms for two minutes before giving such care.
3. The major part of the equipment used for the care of the perineum is individual for the patient.
4. All equipment that is not individual is sterilized.
5. Complete q.4 hours temperature readings are recorded.

The fundamental idea, therefore, upon which the nursing care of the puerperium is based, is that of prevention of infection from the nose, throat, and hands of the nurse to the patient, and of the prevention of infection from one patient to another.

The isolation of infected patients, carriers, and unregistered cases we consider a most important part of the general plan of control. The isolation unit is virtually a small, complete hospital within the main hospital. It can function with complete independence from the main service, since it is equipped with its own pantries, nurseries and delivery-operating room. To this unit are sent all patients who show any evidence of infection, regardless of the cause. Here they are received in an observation ward until a definite diagnosis is established. Cases of puerperal sepsis are further isolated in a smaller ward within the unit especially reserved for them. All patients in the isolation unit are separated by individual cubicles and are handled according to a technic patterned after that in common usage in contagious hospitals. In this way each patient becomes an entirely separate unit, thus eliminating the possibility of cross infections. This last point needs emphasis. If the isolation unit has no provisions for avoiding cross infections, then there will necessarily be great hesitancy about sending the mildly infected case to this unit. Certainly one would hesitate to send a patient with a simple upper respiratory infection to such an unprotected unit. By using the technic described, the patient has practically complete security from cross infections, and we do not hesitate to transfer even normal puerpera to this unit. Normal women, incidentally, who are nursing their babies, may be transferred there with their babies when the latter require isolation. We have not a single recorded instance of an acquired cross infection in this normal group during eight years of operation.

We conclude from this more or less categorical exposition of the subject that prophylaxis against puerperal sepsis is a battle that must be fought on many different fronts. There are no short cuts. It is a battle that requires an organized effort on the part of all, an insistence on uniformity of methods, a loyalty of purpose and, finally, a repetition of details that becomes ritualistic and automatic in performance.

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**Yuki, S.: Another Death of a Fetus After the Administration of Quinine, Jap. J. Obst. & Gynec. 19: 311, 1936.**

The author reports a case of a woman who was given 3 gr. of quinine at 2, 4, and 6 o'clock. She was not in labor. The next morning the patient complained that she could not feel fetal movements. Auscultation failed to reveal the heart tones which had previously been heard. Uterine contractions set in shortly and a still-born child was born. In a case reported by the author in 1934 autopsy revealed changes in the liver and kidneys which could be regarded as having been due to intoxication from quinine.

J. P. GREENHILL.

## SECONDARY PERINEORRHAPHY AT A SUBSEQUENT DELIVERY

HAMILTON V. GAYDEN, M.D., NASHVILLE, TENN., AND  
E. D. PLASS, M.D., IOWA CITY, IA.

*(From the Department of Obstetrics and Gynecology, State University of Iowa,  
Iowa City, Iowa)*

THE immediate repair of perineal injuries incident to delivery has become generally accepted obstetric practice, but it is not yet widely recognized that the unsatisfactory results of previous obstetric trauma, with or without attempted early repair, may be attacked surgically at the time of a subsequent delivery. This report summarizes the results obtained in such secondary repairs of the perineum performed in the University Hospital from July 1, 1926 to Dec. 31, 1934.

Apparently, Bubis,<sup>1</sup> in 1925, first called the attention of the profession in this country to the practicability of repairing old vaginal and cervical lesions at the time of a subsequent delivery and refuted the older ideas that such attempts were unwise because of the edema and friability of the tissues and because the lochial discharges would interfere with healing. His records indicated that the results to be expected were as good as, or better than, those obtained from the more routine surgical attack upon such lesions during an interval between pregnancies. During the past decade, Bubis has elaborated his hypothesis and has received support from the majority of obstetricians who have attempted his technic, although an occasional statement of disagreement has appeared. Before the appearance of Bubis' communication, a small independent experience in the same direction had demonstrated the validity of his conclusions, and it has, therefore, been the practice in the clinic to subject those patients, who show old, symptom-producing perineal relaxations, to immediate postpartum repair, provided no contraindication exists.

The technic of the operation, which is performed immediately after expulsion of the placenta, does not differ from that followed in other secondary repairs, but allowance must be made for subsequent involution. No variations in the usual postpartum care are necessary, except that, after repair of a complete laceration, evacuation of the bowels should be postponed for several days, during which a low residue diet is given.

During the years under consideration, 4,412 patients were delivered, including 1,965 primigravidas and 2,447 multigravidas. Among the

latter group, 161 secondary perineal repairs were performed, an incidence of 0.66 per cent. The operations included:

Repair of old complete perineal lacerations	22
Repair of old incomplete perineal lacerations	128
Repair of anterior and posterior vaginal walls	6
Repair of anterior and posterior vaginal walls and cervix	3
Repair of posterior vaginal wall and cervix	2
	<hr/>
	161

The results of immediate postpartum repairs of old complete tears were compared with those obtained in a consecutive series of secondary repairs of similar lesions on the gynecologic division, where the same technic, performed by the same group of operators, and the same after-care were employed, but where the patients were some months or years removed from the last preceding pregnancy.

Convalescence was judged by the postoperative temperature response according to the following criteria: Mouth temperatures were recorded every four hours, day and night during the patient's stay in bed, and temperatures of 100.4° F. or more were considered abnormal. A diagnosis of "febrile morbidity" demanded that the temperature rise to 100.4° F. or more on any two days after operation, excluding the first twenty-four hours.

Final operative results were judged by two standards: (a) Visual and palpable evidence of proper healing, and (b) the functional capacity of the repaired structures as indicated by the patient's relief from previous symptoms.

#### RESULTS

*Simple Repair of Old Incomplete Perineal Lacerations.*—One hundred and twenty-eight patients were subjected only to secondary perineorrhaphies immediately after delivery (Table I). The hospital stay was hardly prolonged above the average for patients who had recent lacerations repaired. There was no mortality and the total febrile morbidity, 11.7 per cent, was actually lower than the average for the clinic when the same criteria are employed. In four instances, 3.1 per cent, primary healing did not occur, but the final functional result was invariably good.

*Repair of Old Incomplete Perineal Lacerations Associated with Other Plastic Repairs.*—In eleven patients, perineorrhaphy was accompanied by the plastic repair of other injuries from preceding deliveries (Table I). It will be noted that there is a high incidence of one-day elevations of temperature (55.0 per cent), but that the puerperium was "febrile" in only one instance (9.0 per cent). The repairs all healed satisfactorily and the functional results were good (Table I).

*Repair of Old Complete Lacerations.*—During the interval reviewed, twenty-two complete tears sustained at some previous confinement were repaired immediately after delivery on the obstetric division, while the same operators, using identical operative technics and similar after-care on the gynecologic division, attacked sixty complete tears some months or years after the last preceding pregnancy (Table II). The advantages of repairing such old complete tears just after another delivery are reflected in the lower morbidity among the first group, as well as in the higher percentages of satisfactory anatomic healing and of functional restoration.



TABLE I. REPAIRS OF INCOMPLETE PERINEAL LACERATIONS IMMEDIATELY AFTER A SUBSEQUENT DELIVERY

TYPE OF OPERATION	NO. OF PATIENTS	AVER. NO. OF DAYS IN HOSPITAL AFTER OPERATION	MORTALITY	MORBIDITY		RESULTS	
				ONE-DAY FEVER	MORE THAN ONE-DAY FEVER	ANATOMICAL	FUNCTIONAL
Perineorrhaphy	128	12.1	0	12 9.3%	3 2.3%	Good* 124 Fair 4	Good 128
Perineorrhaphy and anterior colporrhaphy	6	13.5	0	3 50.0%	0 0.0%	Good 6	Good 6
Perineorrhaphy, anterior colporrhaphy, and cervical repair	3	14.8	0	2 66.6%	0 0.0%	Good 3	Good 3
Perineorrhaphy and cervical repair	2	13.0	0	1 50.0%	1 50.0%	Good 2	Good 2
Total	139	12.2	0	18 13.0%	4 3.1%	Good 135 Fair 4	Good 139

\*Good, satisfactory

Fair, not completely satisfactory, but not a real failure.

TABLE II. REPAIRS OF COMPLETE PERINEAL LACERATIONS IMMEDIATELY AFTER DELIVERY AS COMPARED WITH SIMILAR OPERATIONS MONTHS OR YEARS AFTER THE LAST PRECEDING PREGNANCY

TIME OF OPERATION	NO. OF PATIENTS	AVER. NO. OF DAYS IN HOSPITAL AFTER OPERATION	MORTALITY	MORBIDITY		RESULTS	
				ONE-DAY FEVER	MORE THAN ONE-DAY FEVER	ANATOMICAL	FUNCTIONAL
Immediately after delivery	22	14.3	0	3 13.6%	1 4.5%	Good* 19 Fair 3	Good 21 Poor 1
Months or years after last preceding delivery	60	17.1	1 1.7%	23 38.3%	12 20.0%	Good 44 Fair 12 Poor 4	Good 52 Fair 6 Poor 2

\*Good, satisfactory

Fair, not completely satisfactory

Poor, failure

The one fatality, E. E., Hospital No. A-6472, among the sixty "interval" repairs done on the gynecologic division, was probably due to pulmonary embolism. Autopsy was not permitted, but death occurred on the twelfth postoperative day within thirty minutes after a sudden attack of dyspnea associated with an imperceptible pulse and other evidence of shock, following a mildly febrile operative convalescence.

#### DISCUSSION

Such results indicate that the older theoretical objections to plastic restoration of the pelvic structures immediately after delivery are unsupported by actual experience and that the probability of satisfactory healing is actually improved at this time. Technically, the performance of perineorrhaphy is simpler by reason of the partial, natural separation of the structural planes and the relaxation of the perineal tissues, while the postpartum hyperemia of the tissues apparently promotes primary union. On the other hand, cystocele repair may be complicated by considerable oozing and by unusual friability of the tissues, making satisfactory closure more difficult; for this reason it should be attempted only by those familiar with pelvic plastic surgery. It should, moreover, be unnecessary to insist that some experience in the usual secondary repair procedures is essential to good results from any gynecoplastic surgery.

#### SUMMARY

In secondary perineorrhaphy performed immediately after a subsequent delivery, the obstetrician has available a procedure, which (1) is technically simple, (2) gives more generally satisfactory results than do similar operations performed some time after the last preceding pregnancy, (3) is economically advantageous for the patient because it avoids a separate hospitalization solely for the repair, and (4) usually does not complicate convalescence nor increase appreciably the duration of postpartum hospitalization.

It is, therefore, recommended for consideration by those who are familiar with the surgical principles involved in the repair of perineal lacerations and relaxations.

#### REFERENCE

- (1) *Bubis, J. L.*: AM. J. OBST. & GYN. 10: 213, 1925.

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**Hauch, B., and Moller-Christensen, E.**: Preliminary Results With Ergometrine, *Acta obst. et gynec. Scand. 16*: 152, 1936.

Studies made by these authors convinced them that Moir's claims are justified. They found that better results were obtained with ergometrine than with corresponding doses of fluidextract of ergot.

J. P. GREENHILL.

## CONGENITAL HYDROPS FETALIS (SCHRIDDE TYPE)\*

HAROLD A. PECK, M.D., F.A.C.S., AND JOHN J. CLEMMER, JR., M.D.,  
GLENS FALLS, N. Y.

*(From the Obstetrical Department of the Memorial Hospital and the Bender Hygienic Laboratory of Albany)*

THE birth of a baby presenting the picture of universal edema is not a new phenomenon, according to reports in the literature going back to the seventeenth century. Its association, however, with a definite blood picture, regular appearing changes in the hematopoietic centers and the finding of extramedullary centers of hematopoiesis is comparatively new. Ballantyne<sup>1</sup> of Edinburgh in 1902 gave a classic description of the condition as he found it and defined it as "a morbid condition of the fetus characterized by general anasarca, by the presence of effusions in the peritoneal, pleural and pericardial sacs, usually by edema of the placenta, and it results in the death of the fetus or infant before, during, or very soon after birth."

Schridde<sup>2</sup> in 1910 found in the cases where there was no anatomicopathologic basis for the edema that there was a consistent finding of an erythroblastosis in the blood, a stimulation of the hematopoietic centers both intra- and extramedullary, and deposits of hemosiderin in some of the viscera, notably the spleen, liver, and kidneys. He considered the condition as the result of an anemia caused by some unknown toxin, probably arising in the fetus.

Baby C., female, premature seven months, stillborn Sept. 11, 1935. The mother, para iv, thirty-four years old, of French-Canadian extraction, married eight years. No living children at present. The first baby, male, born spontaneously, lived to be four years old and died of what was diagnosed as purpura hemorrhagica. From the description of this baby's last illness the diagnosis was undoubtedly correct. The second pregnancy in 1932 ended in spontaneous abortion at two months. The third pregnancy terminated in 1933 was an intrauterine stillbirth. No autopsy. A personal communication from the physician who delivered her stated that the fetus had died a week or ten days previous to delivery and that it showed no signs of edema but was the typical macerated fetus with which we are all familiar.

Present pregnancy: Last normal period Feb. 9, 1935. Expected date Nov. 16, 1935. First seen by the senior author April 24, 1935, with a history of considerable nausea and vomiting but not persistent enough to be classed as pernicious. Considerable headache and dizziness at times. No edema. Wassermann negative. During May and June she was better under careful diet and attention to the emunctories. During July and August much better, quite normal. Fetal life was first felt about the middle of June. Blood pressure during these months varied from 100/70 to 114/70. Urine normal.

About September 1, she began to complain of asthenia, headaches, dizzy spells, edema of the lower extremities and oliguria. Abdomen steadily enlarging. Only one fetal heart heard. Blood pressure rose fairly promptly to 140/96. Urine showed an increase of albumin but no casts. She was put to bed, diet restricted, low protein and salt free. Saline cathartics each morning. This was tried for one week with no regression of the signs or symptoms. Blood pressure increased to 156/106. General condition less favorable. Pressure of the large uterus increasing the dyspnea. On September 9, she was sent to the hospital for induction of labor. Vaginal examination at this time showed the cervix two fingers dilated with the presenting

\*Read before the Eastern New York Obstetrical Society, December 5, 1935.

part fairly high above the brim. It could not be definitely determined whether a deformed head or the breech was in the cervix. Abdominal examination was unsatisfactory on account of the tense uterus. Fetal heart present, 140 per minute. Hydramnios with anencephaly was suspected. Patient was given 10 c.c. of 25 per cent magnesium sulphate intramuscularly every four hours; a milk diet and a retention enema of chloral and bromides were given for sleep. Twenty-four hours after admission the membranes were ruptured and a definite breech made out in the cervix. Blood pressure at this time 160/100. Labor started promptly at 2 P.M. September 10. Delivery of a stillborn edematous fetus, placenta, and cord occurred at 9:36 A.M. September 11. Fetal movement had stopped about 9:30 P.M. on the tenth, and no fetal heart could be elicited thereafter. Two specimens of urine taken while the patient was in the hospital showed traces of albumin with many granular casts on one occasion and only an occasional cast on the second test.

The postpartum convalescence of the mother was quite normal. Urine output increased, edema disappeared, blood pressure came down slowly so that on the twelfth day it was again 110/80. When the patient returned for her six weeks examination, the blood pressure was 116/80, no edema, and urine normal. Her only complaint was moderate asthenia. Blood count showed a moderate secondary anemia.

#### COMMENT

While the first-borns are usually spared from these blood dyscrasias, from the outcome of the first baby in this case followed some time later by another showing definite signs of erythroblastosis, I wonder if the first-born might not have been one of the cases of congenital anemia or erythroblastic anemia which eventually became purpuric.

*Autopsy.*—Gross and microscopic description. The body was that of a premature stillborn infant, having a crown-rump measurement of 27 cm., indicating a fetal age of about seven months. A large edematous placenta weighing 900 gm. and an umbilical cord 130 cm. in length were attached. There was an extremely marked generalized edema of the subcutaneous tissues. The soft tissues of the face were swollen, compressing the eyelids. The labia were tense with fluid. Large ecchymotic bullae were present over the lower extremities. The peritoneal cavity contained about 250 c.c. of clear serous fluid and each pleural cavity about 75 c.c. The pericardial fluid was not excessive.

The heart was of normal size and shape. The myocardium was firm and dark red. The foramen ovale and ductus arteriosus were patent. The lungs were atelectatic. The liver and spleen were moderately enlarged. The hepatic parenchyma was dark red and the lobules indistinct. The splenic pulp was soft and homogeneously red. The kidneys appeared congested. The thymus gland was smaller than normal. The medulla of the femur was filled with soft red cellular marrow.

*Histology.*—*Liver:* (Figs. 1 and 2.) The principal histologic findings in the liver were marked erythroblastosis and very heavy deposition of hemosiderin pigment. Diffuse hemopoiesis was observed between the reticulum lining the liver capillaries and the cords of hepatic cells. The majority of the blood cells were megalo-blasts and normoblasts. The former presented large vesicular basophilic nuclei containing nucleoli with a narrow rim of clear neutral cytoplasm. The normoblasts exhibited small round hyperchromatic nuclei with a rim of light blue to brown cytoplasm. Several of the cells were undergoing nuclear division. Small numbers of various types of myeloid cells were scattered among the erythropoietic tissue. The liver cords were shrunken as though by pressure of the adjacent hematopoietic cells. The cytoplasm of the hepatic cells was heavily laden with brown pigment which gave the Prussian blue reaction for hemosiderin. The reticulo-endothelial cells contained little demonstrable pigment. The sinusoids were dilated and the blood in them showed many primitive nucleated cells.

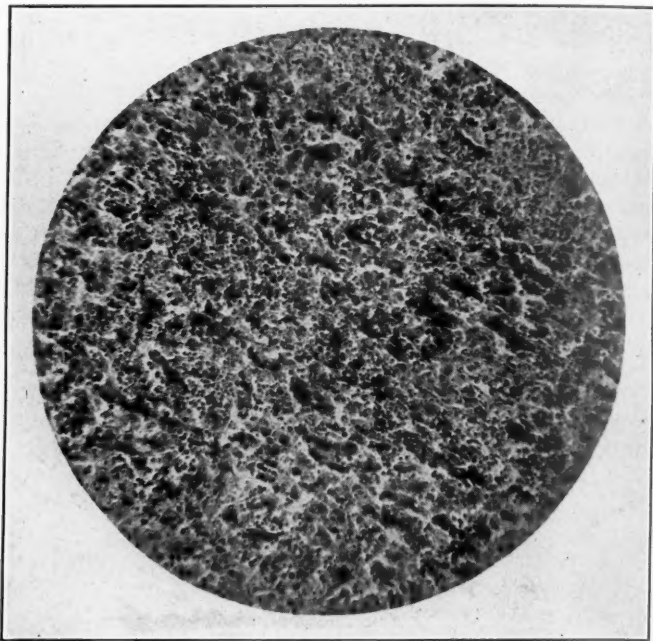


Fig. 1.—Marked diffuse hemopoiesis of liver. Dark granules in hepatic cells represent hemosiderin.  $\times 120$ .

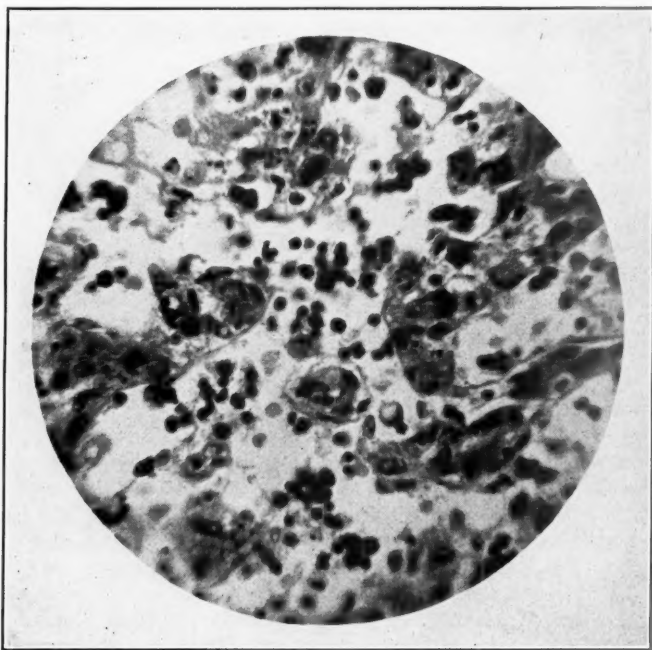


Fig. 2.—Numerous megaloblasts and normoblasts between reticulum lining and hepatic cell cords and in liver sinusoids. Note amitotic division of nuclei in some of the normoblasts.  $\times 500$ .



*Spleen:* (Fig. 3.) The spleen showed diffuse hemopoiesis, the predominating cells being erythropoietic. Lymph follicles were not present. The splenic reticulum was prominent and the sinusoids appeared distended. Many of the reticulo-endothelial cells were enlarged and filled with brick red pigment which failed to give the Prussian blue reaction for iron. It was considered to be hemoglobin.

*Bone Marrow (Femur):* (Fig. 4.) The spaces between the bone trabeculae were filled with blood cells, chiefly erythrocytic. Normoblasts, erythrocytes and megakaryocytes composed the marrow in about the order named, with a few intermingled myeloid cells, megakaryocytes and lymphocytes. Free blood pigment was not demonstrable here.

*Kidneys:* (Fig. 5.) The architecture of the kidneys was of the fetal type with large hyperchromatic glomerular tufts and a moderate amount of loose interstitial tissue, particularly noticeable in the medullary portions. The striking finding was

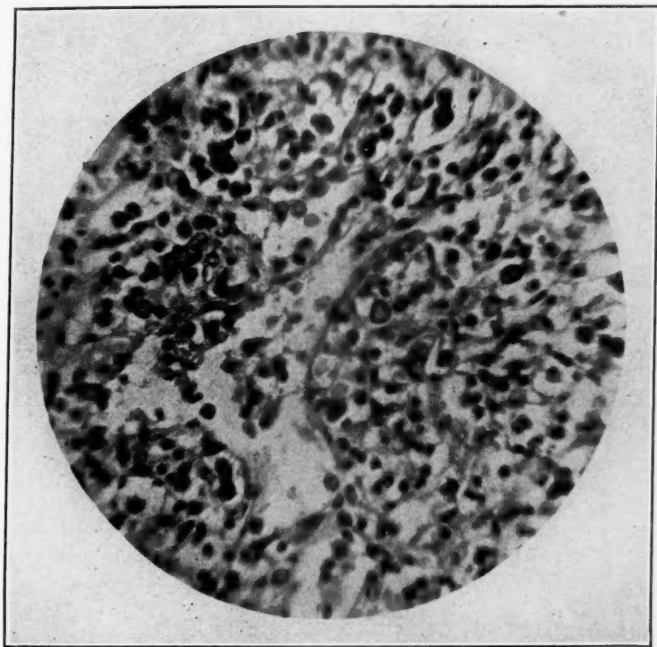


Fig. 3.—Spleen. Note enlarged reticuloendothelial cells and many nucleated erythrocytic cells.  $\times 500$ .

the presence of large amounts of brick red granular pigment in the lining cells of the convoluted tubules. This pigment like that in the spleen proved to be hemoglobin. A few of the smaller collecting tubules contained hyaline casts.

*Blood Smear (Umbilical Cord):* (Fig. 6.) A Wright's stained smear of blood collected from the cord vessels at the time of delivery revealed 11 per cent megakaryoblasts, 17 per cent normoblasts, and 72 per cent erythrocytes among 500 cells of the erythrocytic series. Leucocytes were very rare. Of those present, about 65 per cent were lymphoid and 35 per cent myeloid.

*Other Tissues:* The lungs showed atelectasis. Erythropoietic cells, principally intravascular, were observed in all of the organs. A section of abdominal skin (Fig. 7) showed marked edema of the subcutaneous tissue with small focal hemorrhages. The placenta exhibited edema of the connective tissue in some of the chorionic villi.

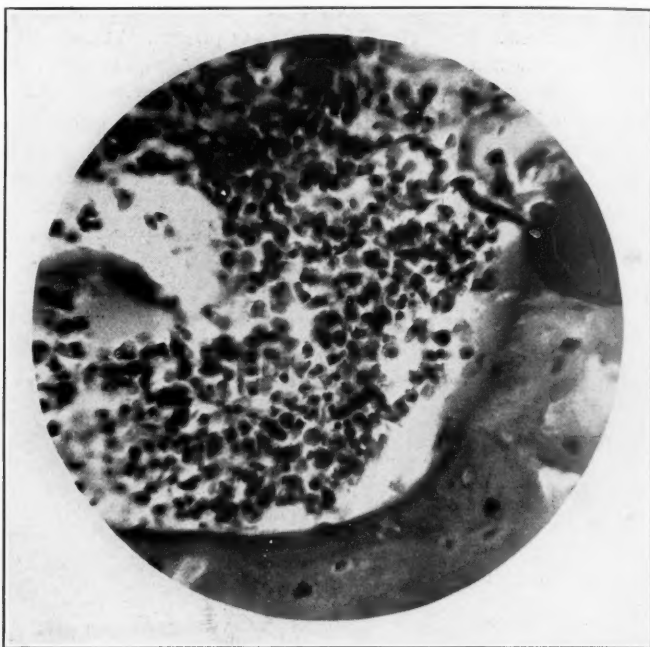


Fig. 4.—Bone marrow (femur). Marked hemopoiesis, chiefly erythrogenic.  $\times 500$ .

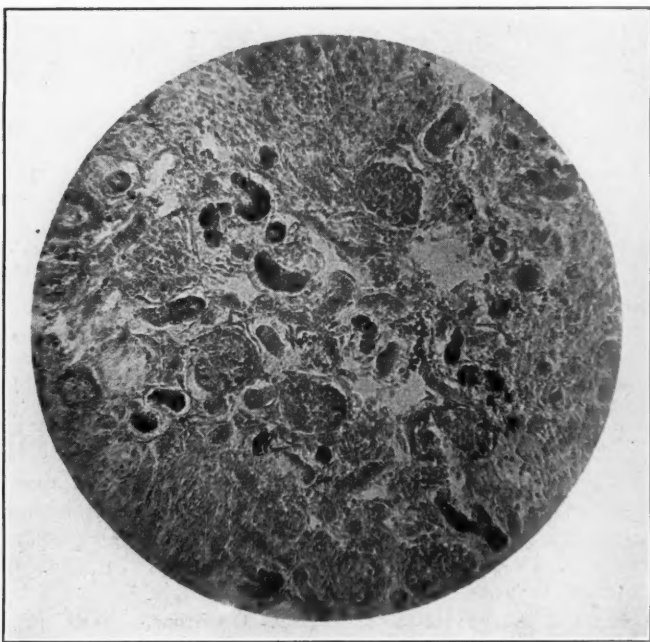


Fig. 5.—Large amounts of brick red granular pigment (hemoglobin) in lining cells of renal tubules. The pigment appears as closely packed black granules in this microphotograph.  $\times 120$ .

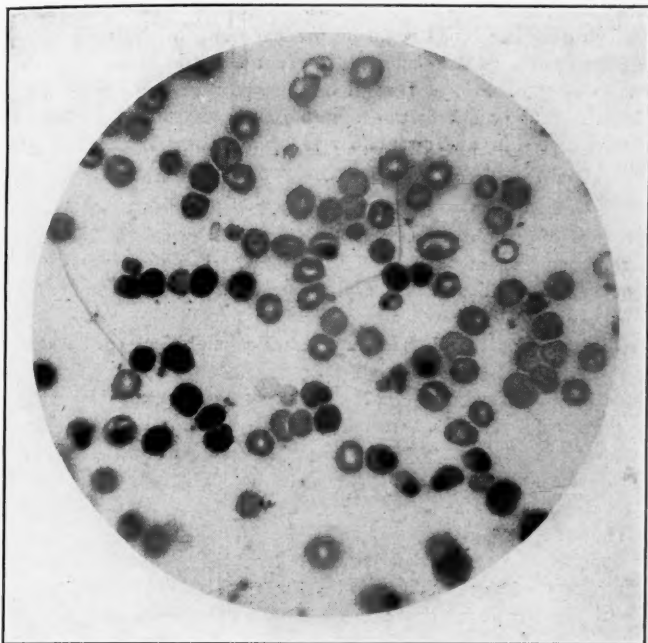


Fig. 6.—Blood smear (umbilical cord) showing high percentage of erythropoietic cells. The cells with large nuclei and little cytoplasm are megaloblasts; those with small round nuclei and much cytoplasm, normoblasts. Intermediate forms may be termed erythroblasts.  $\times 500$ .

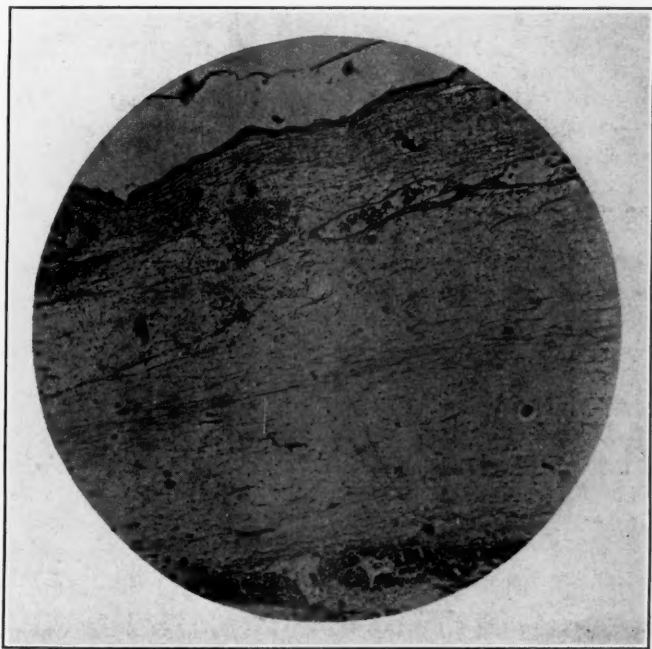


Fig. 7.—Abdominal skin. Marked edema of subcutaneous tissue with small focal hemorrhages.  $\times 50$ .

*Pathologic Summary.*—Marked generalized anasarca, blood pigment deposition, and erythroblastosis. The blood pigment predominated in the liver as hemosiderin and in the lining cells of the convoluted renal tubules as well as the reticulo-endothelial cells of the spleen as hemoglobin. Erythroblastosis was strikingly present in the bone marrow, the liver and the spleen. The heart, thymus gland, lymph nodes, kidneys, lungs, skin, and circulatory blood contained erythropoietic cells.

#### DISCUSSION

The presence of erythroblastosis may be suggested by the finding of generalized anasarca, icterus or anemia in a newborn infant. The demonstration of a high percentage of nucleated cells of the erythrocytic series in a smear of blood from the infant or the umbilical cord is a reliable confirmatory test. Recent studies made at the Bender Hygienic Laboratory in which umbilical cord smears were examined from 59 normal cases showed in each instance less than 0.5 per cent of the erythrocytic cells to be nucleated. Megaloblasts were practically absent and in most of the smears normoblasts were encountered rarely. This is in sharp contrast to the cord smear in the case presented in which 28 per cent of the erythrocytic cells were primitive nucleated ones. The wide dissemination of erythroblastosis in various body tissues studied at necropsy indicates that this was an important feature of the disease.

We have mentioned several theories that have been postulated concerning the nature and etiology of erythroblastosis in the newborn. However, none of these explain why in some cases anasarca is strikingly prominent, in others icterus and in still others anemia. May we offer the following hypothesis for consideration.

Erythroblastosis with anasarca develops during fetal life, the afflicted only occasionally progress to term and have never been known (reported) to live more than six days after birth. Apparently the destruction and excessive production of erythrocytes is very deleterious when it occurs in early fetal life. Perhaps the deposition of hemoglobin in the renal epithelium and the continued effort to excrete this pigment may impair developing kidneys with resultant damming back of fluid excretion.

If the condition develops later in intrauterine life, the fetal kidneys are better prepared to perform their task. However, if the erythroblastosis and destruction of erythrocytes progress to a fulminating degree, the patient will develop severe jaundice and succumb to icterus gravis.

The cases of congenital anemia (Cooley's anemia) which have been classed in this group are of a much milder nature than those exhibiting anasarca or icterus. They are often apparently normal full-term infants who develop marked pallor and anemia, some times with slight jaundice several days after birth. Most of these patients recover. As the erythroblastosis and destruction of blood corpuscles occur relatively late in life, we would expect the infant to more successfully cope with the disease.

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## RADIUM THERAPY IN GRANULOSA CELL TUMOR OF THE OVARY

WILLIAM E. STUDDIFORD, M.D., NEW YORK, N. Y.

RECENTLY in listening to a general discussion of ovarian tumors by Pemberton,<sup>1</sup> a patient with a granulosa cell tumor was mentioned, who, unfit for operation, was receiving radium therapy. The speaker stated that he had been unable to find any information on the effect of radium on these tumors. Novak and Brawner<sup>2</sup> state that few reports have been made on this form of treatment. In view of this, it was felt that the following case would be of interest.

Mrs. G. M., aged sixty-seven years, widow, para ii, gravida ii. Menopause at forty-four years of age. No bleeding until present history. No menopausal symptoms. On June 7, 1933, she had vaginal bleeding which persisted for a month. The patient was treated by Dr. Charles Larkin of Waterbury, Conn. He performed a curettage and cauterized several nabothian cysts. Following this 100 mg. of radium were placed in the uterus and left for thirty hours. Sections of these curettings showed hyperplastic endometrium with no evidence of malignancy. At the time of the operation there was noted a small fibroid on the right side of the fundus. No further bleeding occurred, but on return to Dr. Larkin on June 26, 1934, he found a cyst of the left ovary which was described as being about the size of an orange. He noticed at the time that the uterus was small and in good position. He advised operation but the patient ignored this advice. She was seen for the first time by the author on March 1, 1935, when she stated that she had been bleeding for about one month.

The patient was an elderly female who appeared in excellent condition. General physical examination negative except for slight thickening of brachial arteries.

There was an elastic mass which rose out of the pelvis about halfway to the umbilicus. A cystocele of moderate degree and a small rectocele were present. The cervix was posterior and normal except for small scar on the posterior lip. A cystic mass arose from the left adnexa and passed in front of the uterus. It was continuous with the mass felt abdominally. Blood pressure 150/72. Urine examination negative.

On March 11, 1934, following a curettage, a laparotomy was performed and a left ovarian tumor measuring 14 by 11 cm. was removed together with the tube. The right ovary was extremely atrophic. The uterus lay behind the tumor and appeared only slightly smaller than the organ of a female in active sexual life. Nothing further was done and the abdomen was closed. Convalescence was uneventful, the patient being discharged on the seventeenth day.

A hormone study was made by Dr. Raphael Kurzrok on the urine collected during the first twenty-four hours after operation. At least 8 rat units of female sex hormone per liter were found.

*Pathologic Examination.*—Ovary irregular, soft, cystic, mass 14 by 11 by 6 cm., greenish purple color, and made up of several loculi. On one surface was a small cystic area, contents of which have been evacuated; it apparently measured about 3 cm. in diameter. On section tumor was made up of numerous small cystic areas, the largest being approximately 4 cm. in diameter. The lining of these cystic areas was smooth, and they contained thin bloody fluid. Major portion of tumor, however, was formed by soft friable solid tissue which in turn had numerous minute cysts scattered throughout.



*Microscopic Examination.*—(a) Tissue was covered by single layer low columnar cells, showing very slight infolding. Underlying glands were rather numerous; they varied considerably in size and shape, many being small and round and others showing slight cystic dilatation. Glands were lined by single layer low columnar cells; in some areas this epithelium was quite edematous. Supporting stroma was moderately dense and in most of the section showed considerable edema. Numerous lymphocytes were seen throughout the stroma (Fig. 1). (b) Stroma was dense and fibrous; in many areas it was quite edematous. Blood vessels were engorged. Numerous corpora albicantia were seen throughout the stroma. For most part the ovary was replaced by rather solid masses of tumor cells which were small and deep staining, resembling granulosa cells of normal follicle. The cells were compactly arranged and showed little variation in staining properties; occasional mitosis was seen. In some areas small glandlike or cystic spaces were noted lined by single layer small cuboidal cells; this layer of epithelium was directly supported by the tumor cells. The cells invaded the stroma in many places; in more solid areas fine fibrous



Fig. 1.—Microphotograph of endometrium showing moderate hyperplasia.

connective tissue stroma was seen. Other sections showed larger cystic areas similar to those described, in which considerable necrosis and degeneration were noted. In some places normal ovarian stroma was markedly edematous and contained considerable extravasation or red blood cells along with hemosiderin deposits (Figs. 2 and 3).

*Diagnosis.*—(a) Glandular hyperplasia of endometrium. (b) Granulosa cell tumor, left ovary.

This patient was seen again on April 15, 1935. Her operative incision was well healed. There was no evidence of recurrence of the tumor. The uterus was extremely small. She was last seen on Feb. 26, 1936. No change was found as compared to her previous visit. She stated that she was having marked hot flashes and was extremely nervous. She had never experienced these symptoms before although her menopause had occurred at the age of forty-four years.

In view of marked sensitivity of the follicular system to radium therapy, the use of this form of treatment is immediately suggested in the granulosa cell tumor. This case, therefore, is of considerable interest. At a stage when the tumor was too small to be easily detected clinically, radium therapy was utilized. The sup-

position that the tumor was present at this time rests on fairly good grounds, inasmuch as the patient was bleeding from a hyperplastic endometrium at the age of sixty-five. The dosage of 3,000 mg. hours which was used is sufficient to completely destroy the follicular system in a young woman. However, while uterine bleeding

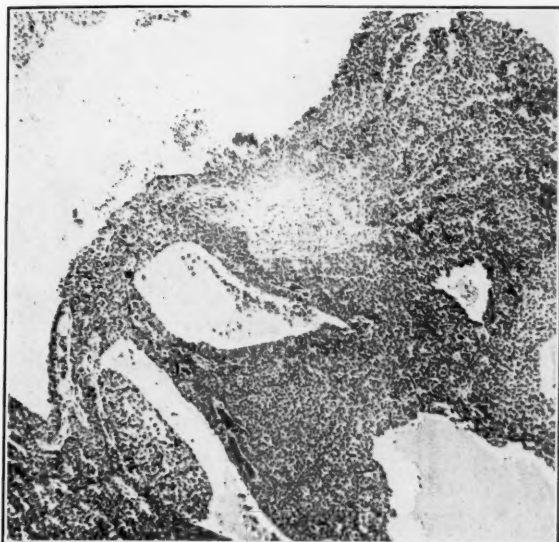


Fig. 2.—Low power microphotograph showing typical arrangement of granulosa cell tumor with folliculoid spaces.

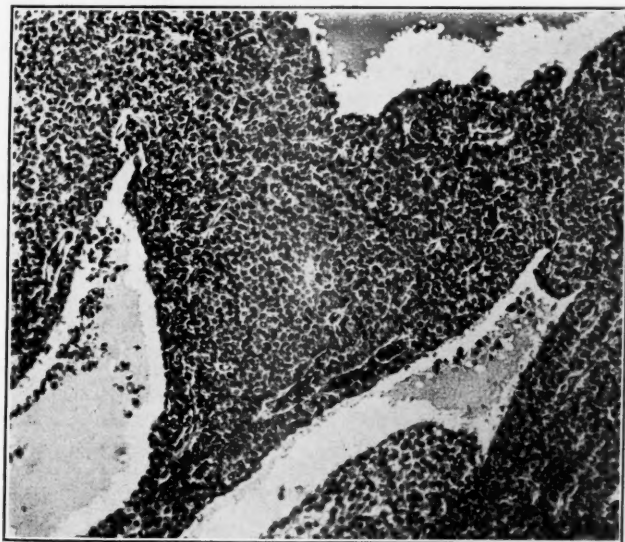


Fig. 3.—High power microphotograph of same field.

ceased, the tumor continued to grow and was first noted clinically about one year later. About twenty-one months after the use of radium, the tumor was large enough to be apparent on abdominal inspection and uterine bleeding had recurred. The histologic appearance of the tumor and the hormone findings in the urine to-

gether with the appearance of the endometrium show that in this particular case radium had no effect other than to mask the clinical picture by temporarily controlling the uterine bleeding. That this form of therapy did not affect the functional activity of this tumor, even for a short period, is suggested by the fact that menopausal symptoms appeared for the first time after the complete surgical removal.

While one is not justified in making assumptions on the basis of one case, nevertheless the following conclusions are suggested:

1. Radium, while very destructive to the normal follicular system in large doses, does not have the same effect on neoplastic granulosa cells.
2. Bleeding, accompanied by benign endometrial hyperplasia, in the postmenopausal woman, strongly suggests the presence of granulosa cell tumor. A laparotomy is justified in the presence of these findings.
3. The treatment of this type of tumor is surgical, unless there are strong contraindications to operation.

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### PLACENTA ACCRETA FOUND AT CESAREAN SECTION

ALBERT MATHIEU, M.D., F.A.C.S., PORTLAND, ORE.

FORTUNATE indeed is the one who finds placenta accreta at cesarean section rather than following vaginal delivery of the baby. Phaneuf<sup>1</sup> in 1933 collected 82 cases of placenta accreta and stated that the mortality rate was 72.1 per cent in cases where manual extraction of the placenta was done through the vagina; 5.8 per cent following delivery by vagina in cases where the diagnosis was made sufficiently early and in which abdominal hysterectomy was done; and 36.3 per cent in those cases of a similar class in which vaginal hysterectomy was done. From this follows the fact that the earlier abdominal hysterectomy is done after the discovery of the placenta accreta, the lower the mortality rate will be. I have been able to find in the literature eight cases of placenta accreta which were found during cesarean section (Table I). In all these cases, except one, immediate supra-vaginal amputation of the fundus was done with the result that all mothers and all babies lived. The following description of my case helps to substantiate the belief that practically all cases of placenta accreta are associated with other anomalies, the most common of which are the results of injuries to the endometrium by medication or instrumentation, fibroids of the uterus, diseases of the endometrium, placenta previa, or anatomic anomalies of the uterine body. As will be seen in a study of this case, there was a peculiar combination of abnormal circumstances.

#### CASE REPORT

A forty-three-year-old primipara was first seen by me June 6, 1925. Her history was negative except for a right oophorectomy four years before. Her last menstrual period was on Dec. 22, 1924. Physical examination at the time she consulted me revealed a six months' pregnancy with no abnormalities demonstrable, except a cyst of the cervix and a moderate anemia. At the end of her eighth month, Aug. 28, 1925, examination with a speculum revealed that the cyst on the cervix had increased considerably in size. It was as large as a lemon and over its posterior

surface extended a vein as large as a match. Neither with the speculum nor with my finger by manual examination could I find the external os or any sign of a cervical opening. Apparently this must have been a pinpoint opening. The breech was below. The blood pressure was 110/60. The urine examination showed a slight trace of albumin. The height of the fundus was 34 cm. The patient had considerable pain in her back and sides. Because of the cervical cyst with the large vein on its posterior surface, the apparent stenosis of the cervix, the breech presentation, and the fact that the patient was a primipara at forty-three years of age, I decided to do a cesarean section at term.

The patient was examined at weekly intervals. The blood pressure remained at approximately 120/80. The height of the fundus increased to 36 cm. The baby remained in breech presentation. The urine was consistently negative. The cyst of the cervix, however, seemed to be growing in proportion to the growth of the uterus, so that at the time of the operation it practically filled the entire upper vaginal tract.

Several days before the estimated date of confinement a classical cesarean section was started, and the abdomen was opened to the right of the umbilicus for a distance of 12 cm., one-half above and one-half below the umbilicus. The uterus was opened and a male child weighing 4,285 gm. was extracted. On attempting to remove the placenta it was found to be grown into the myometrium and attempts to wipe it loose with a towel were of no avail. At each effort masses of placental tissue were left attached to the uterus. As considerable blood was being lost during the procedure, a rapid supravaginal hysterectomy was performed. At this time an effort was made from above to find a cervical opening inside the uterus, but none was apparent.

The patient suffered severe shock during the operation, but following a blood transfusion she had a normal postoperative course. On the twelfth postoperative day, because of severe backache, a vaginal examination was made. It was found that the cervical cyst had shrunk to the size of an egg; and a small dimple, which was probably the external os, could be felt. In the beginning of the third week she developed a phlebitis in the left leg with a fever of 101° F. This subsided gradually, and she left the hospital after a stay of forty-seven days with her left leg slightly swollen. Eight months after the cesarean section, examination revealed that the cyst was practically gone and only a very small external os could be seen.

The pathologic report on the removed specimen was: *Gross Examination:* Fundus of the uterus with placenta attached has been removed. Parts of placenta are very firmly attached to the uterus. No lines of demarcation can be made out on gross examination. The placental substance has apparently grown directly into the uterine tissue. A number of fibrous infarcts are present about the borders of the placental substance and they also have a very close contact with the uterine wall. The placenta is apparently no larger than normal size. Cord attachment is about two inches from one border. Cut sections through the placental substance show it to be apparently normal. *Microscopic Examination:* Section through the placenta and uterine wall shows no distinct line of separation. The covering of the placental villi is continuous with the connective tissue stroma of the uterine musculature. Some of the chorionic villi are in the formation of islands which are entirely surrounded by uterine muscle. The condition is characteristic of that described by Polak and Phelan<sup>2</sup> as placenta accreta.

*Diagnosis:* Placenta accreta.

#### SUMMARY

A review of the literature (Table I) revealed that eight cases of placenta accreta had been found at cesarean section, and a study of these cases showed that varied complications preceded or accompanied each one.

Herein is described the ninth case, a primipara, aged forty-three years, with the baby in breech presentation, a large cyst of the cervix almost filling the upper vaginal tract, and an almost complete stenosis of the cervical canal.

Because of these complications a cesarean section was done and the placenta accereta found.

TABLE I. PLACENTA ACCRETA FOUND AT CESAREAN SECTION

NO.	AUTHOR	FATE*		COMPLICATIONS	OPERATION
		M	C		
1	Kwartin and Adler <sup>3</sup>	L	L	Previous section Threatened rupture Hourglass contraction Thin scar	Supracervical hysterectomy
2	Solomons <sup>4</sup>	L	L	Asymmetry of face of fetus Former dead baby Abortion Premature rupture of membranes	Hysterectomy
3	Reeb <sup>5</sup>	L	L	Former premature birth Curettage Hemorrhage Inversion of uterus Salpingitis Peritonitis	Subtotal hysterectomy
4	Neumann <sup>6</sup>	L	L	Twin pregnancy (one fetus pyraceus) Abortion one year later Placenta previa	Hysterectomy
5	Neumann <sup>6</sup>	L	L	Abortions	Manual removal of placenta
6	Joachimovits <sup>7</sup>	L	L	Placenta previa Osteomalacia Contracted pelvis Atony	Hysterectomy
7	Bakanow <sup>8</sup>	L	L	Perforation of uterus Ruptured uterus (due to growth of placenta through uterine wall)	Supravaginal hysterectomy
8	Breuer <sup>9</sup>	L	L	Placenta previa Previous adherent placenta Vaginal infection (thrush) Bicornate uterus	Hysterectomy

\*Fate: M—mother; C—child; L—lived.

A supravaginal hysterectomy was performed followed by a blood transfusion. When the fundus of the uterus was removed, an opening in the cervical canal from the inside could not be located. Both the mother and the baby lived.

Examination of the mother some months after operation showed that the cyst of the cervix had disappeared entirely and that the cervix had assumed its normal configuration.

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## PREGNANCY COMPLICATING NEUROFIBROMATOSIS WITH ASSOCIATED INTRATHORACIC TUMOR

HUGH B. McNALLY, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, School of Medicine, University of Maryland)

**A**LTHOUGH there are comparatively few cases of pregnancy complicating neurofibromatosis reported in the literature, the entire subject has been so completely reviewed and presented in the recent articles by Sharpe and Young and Kushner, that, to do so again would be useless repetition, therefore it is wished only to add one more case report as an additional observation of this interesting phenomenon.

Kushner, Hirsch, Nishizaki, Sharpe and Young have reported cases of neurofibromatosis aggravated by pregnancy. Sutton reports a case which subsided after pregnancy. Others have reported cases in which there was no change following pregnancy as is true of the present case. Wise and Eller observed a case appearing at the time of childbirth. The consensus of findings seems to indicate that pregnancy may reveal otherwise latent neurofibromatosis, that it may definitely aggravate preexisting disease and that following pregnancy symptoms may subside only to reappear with a succeeding pregnancy. The offspring may or may not show manifestations of the disease.

H. C., colored, aged twenty-one, primigravida, was admitted to the University Hospital at term, complaining of progressive weakness of the lower extremities and inability to walk. Her family history was noncontributory and her past history was negative except for the skin lesions which are characteristic of the condition and which had been present since early childhood. One year ago her legs suddenly became weak and the weakness progressed until she found she could not walk. She was seen in another hospital where a diagnosis of mediastinal tumor was made and exploratory operation advised. A large imbedded tumor was found pressing upon the upper dorsal and lower cervical vertebrae, biopsy diagnosis was that of neurofibromatosis (von Recklinghausen's disease). Despite the fact that no attempt was made to remove or change the position of the tumor, the original symptoms almost entirely disappeared, and she was fairly comfortable until about the thirty-sixth week of gestation when the symptoms reappeared and she was admitted to this hospital for study. Her past history prior to the original attack had been negative except for the skin lesions as noted above.

On admission, physical examination revealed a well-developed young colored woman whose whole body surface was covered with numerous macular, dark brown, pigmented areas which stood out prominently on her brown skin; they varied from 1 to 2 cm. in diameter. The lesions were not tender or painful and were circumscribed by an area of pigmentation lighter in hue although still darker than the surrounding skin. There was some limitation of expansion of the right chest and percussion note was slightly impaired at the base on this side. The abdomen contained a full-term pregnancy.

*Neurologic Examination.*—Muscle power, tone, and development of the upper extremities was in no way affected. All deep reflexes in the upper extremities were within normal limits. There was no disturbance of sensation. There was very marked weakness in both lower extremities. There was a slight hypertonicity of the lower extremities. Sensation: there was definite hypoesthesia to all forms of stimulation below the lower distribution of the third dorsal segment. Muscle sense of the

lower extremities not disturbed. Reflexes: all deep reflexes in the lower extremities were hyperactive. There was a positive Babinsky and Oppenheim on the left and positive Chaddock on the right. Ankle clonus strongly suggestive on the right. The abdominal reflexes were absent. Pain perception above the level of the third dorsal segment distribution was felt more clearly and promptly.

Roentgen examination of the chest failed to reveal a tumor but did reveal a marked scoliosis of the lower cervical and upper dorsal region of the spine.

*Clinical Impression of the Neurologist.*—Pressure against the spinal cord at the level of about the fourth dorsal segment.

Because of the above findings and because sterilization was strongly advised, delivery through the abdominal route was elected and she was so delivered of a full-term, living child which was normal in every respect. After her recovery it was found that she could walk a little but that there was still considerable weakness of the lower extremities. Two weeks after her operation an exploratory operation of her chest was performed and a dense massive intrapleural tumor was found. There was definite evidence of pressure over the region of the fourth dorsal vertebra. The tumor was entirely immobile and biopsy was taken. She was discharged with no change in symptoms.

*Pathology.*—Sections from the biopsy showed a mass composed of interlacing hyaline fibers between which lay elongated and spindle cells. There were many normal nerves and large encapsulated areas in which the nerve cells were compressed by intermingling hyaline fibrillae presenting an almost solid and nodular growth. A portion of the pleura attached to the growth showed a mild lymphocytic infiltration. There was no histologic evidence of malignancy.

Examination of the patient eight months later revealed the skin lesions still present but having subsided roughly to the extent of 40 per cent. The patient had been bedridden for the last six months and neurologic signs were accentuated to a marked degree. There was complete paralysis of both lower extremities; all forms of sensation were absent. Muscle sense of the lower extremities showed no change. The Babinski sign was strongly positive on both sides. A beginning atrophy of the lower extremities was noted. The systems otherwise were entirely normal. The baby showed no pathologic signs whatsoever, had progressed normally in weight and gave the general picture of a normal, healthy infant.

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Digonnet, Chenebault and Rouchy: Two Cases of Puerperal Phlebitis Treated by Novocaine Injection of the Lumbar Sympathetics, Bull. Soc. d'obst. et de gynec. 25: 215, 1936.

The authors report two cases of phlegmasia alba dolens which occurred during the puerperium and which they treated therapeutically according to the technic of Leriche, namely, by the injection of novocaine into the lumbar sympathetic system. The authors describe their technic in detail. They observed an immediate beneficial effect. The patient experienced a noticeable increase in heat and a rapid subsidence of the pain. The course of the phlebitis was considerably shortened.

J. P. GREENHILL.

## TWIN PAPYRACEOUS FETUSES IN A TRIPLET PREGNANCY

R. M. COLLINS, M.D., COUNCIL BLUFFS, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa)

FETUS papyraceous (or compressus) is a well-recognized and not uncommon condition. In the usual case, one child of a twin pregnancy (usually binovular) dies from lack of nourishment at approximately the middle of the gestation period and becomes compressed between the amniotic sac of the surviving fetus and the uterine wall. Partial mummification ensues and at delivery the outlines of the fetus are visible in the membranes. Much more rarely, as in the following case report, a triplet pregnancy goes to full term with twin papyraceous fetuses and a single living child.

A. W., Hospital No. K4482, white, married, aged thirty-four years, was admitted to the University Hospital Sept. 20, 1934. Four previous single pregnancies had



Fig. 1.—Photograph by reflected light. The placenta of the normal child is on the left, with the papyraceous fetuses in the center, and the atrophied placenta of the twins in the retracted tissue on the right.

ended in the birth of normal children. In 1925, two partial thyroidectomies had been performed for cosmetic reasons, because of a large symptomless goiter. The last menstrual period began on Jan. 1, 1934, with the expected date of confinement Oct. 8, 1934. The pregnancy had been uneventful except for moderate nausea during the first trimester, and there had been no reason to suspect multiple pregnancy.

Examination revealed an apparently normal uterine pregnancy practically at term. Pelvic measurements were normal. There was a large adenomatous goiter associated with slight tachycardia (pulse rate, 90 to 130 per minute) and a basal metabolic rate of plus 46 per cent. Laboratory findings, including the blood Wassermann, were negative.

Following medical induction of labor with castor oil, quinine, and pituitary extract, labor pains began at 7:00 A.M. Sept. 26, 1934. The fetus lay in L. O. A. and the head was fixed. At 8:10 A.M., the membranes were ruptured artificially to stimulate contractions. At 10:00 A.M., when the cervix was dilated to 5.0 cm., rectal examina-

tion revealed a hand and arm down beside the head. Under ethylene anesthesia, the extremity was replaced and a large Voorhees' bag introduced. At 12:30 P.M., with the cervix fully dilated, the bag was expelled and the head descended to the pelvic floor. Delivery occurred spontaneously at 1:15 P.M. The third stage was normal with less than the usual blood loss, and the puerperium was afebrile.



Fig. 2.—Photograph with transillumination. The relationships are as in Fig. 1.



Fig. 3.—Roentgenogram. The relationships are as in Figs. 1 and 2.

The child, a normal male, weighed 3,650 gm. There was no asphyxia. The post-natal course was uneventful.

Routine examination of the secundines, which weighed 735 gm., revealed the conditions apparent in Fig. 1. In the membranes, a few centimeters from the edge of the mature placenta, two compressed fetuses of approximately the same size lay side by side, while beyond them was the compressed, atrophic placenta to which they were

attached. A photograph, with a strong light source beneath the specimen, Fig. 2, showed the relationships more clearly, while the roentgenogram, Fig. 3, demonstrated the approximately equal development of the two compressed fetuses. The specimen was preserved intact and no attempt was made to determine by histologic examination of the membranes the essential character of the twin development, although it seems more probable that they were uniovular.

We are indebted to Mr. Frederick W. Kent, University Photographer, who took the photographs, and Mr. R. M. Tarrant who made the x-ray film.

## AN INTERNAL AND OUTLET PELVIMETER, COMBINED

LESTER R. MELLOR, M.D., SYRACUSE, N. Y.

THE taking of the outlet as also the internal pelvic measurements in the past has usually been found very unsatisfactory. This fact has been observed quite generally by both obstetricians and general practitioners who have been doing maternity work.

These measurements which are so essential to the practice of good obstetrics have repeatedly been found wrong, due to various causes. First, the careless localizing of the anatomic points from which these measurements are taken. Second, the use of instruments which, although theoretically perfect, are practically of little value for everyday use.

Realizing the above difficulty and striving for better technic in this procedure, during the last few years, I have combined the best points of several instruments and, with essential changes, have developed the present combined instrument.

This instrument (Fig. 1) is made up of three parts: (1) a long curved four-sided section with the centimeter measure upon the front and back in the proper position for reading when in use, (2) a transverse, telescoping section fitted to slide upon the long piece, and (3) a short piece with an upright arm, which also slides on the long section, after removing the transverse member. The long section, with the transverse member fitted upon it, makes an outlet pelvimeter, while the small member replacing the transverse upon the long section becomes an instrument for internal pelvimetry.

The taking of the diagonal and true conjugate is usually a difficult and at times impossible undertaking, either with or without instruments, due to various reasons. First, in primiparas, the firm perinei interfere with the necessary upward pressure which the examining fingers must make to reach the promontory of the sacrum; second, the tilt of the pelvis makes it impossible to measure at times; third, a presenting part in the pelvis may make it impossible; fourth, some multiparous women have firm perinei which make the measurement difficult to take; fifth, pain, caused by the examination, may make it impossible without an anesthetic.

Naturally, if the promontory of the sacrum cannot be reached by the fingers of the examining hand, then one cannot hope to apply an instrument by hand to that point and be sure that it has reached its goal and, vice versa, if one can reach it with the tip of the examining finger, then it can be measured more accurately with an instrument.

I have repeatedly demonstrated the above observations to students, internes, and some fellow practitioners, also the possibility of confusing sacral ossifications with



the true promontory of the sacrum. Naturally in multiparous women one has less difficulty in obtaining the diagonal and true conjugate because of the relaxation of the pelvic structures.

In using my instrument, the first three measurements, diagonal conjugate, true conjugate, and thickness of the pelvic bone are obtained as follows:

The small piece of the instrument is placed upon the long section which is held with the curve upward so that the upright arm is nearest to the curve. (Fig. 2). After examining and ascertaining the position of the promontory with the two examining fingers, the instrument is inserted alongside of the fingers with the curve upward and the shoulder inward. The instrument is worked into place past the side of the cervix upward to the promontory, placing and holding the shoulder of the instrument in place with the fingers or fingernail of the middle finger in the depression behind the upper end of the shoulder of the instrument. The left hand adjusts the upright sliding section beneath the pubic bone and the diagonal conjugate measurement is read off on the long section in centimeters. Then the left hand elevates the upright arm within the vagina and against the pubic bone; with

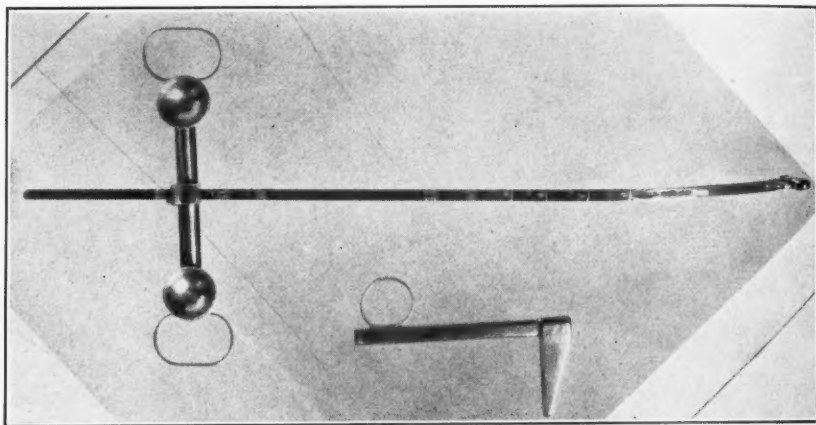


Fig. 1.—Internal and outlet pelvimeter. The long curved section has a transverse section slipped upon it for outlet measurements. The small section is slipped upon the long section after removal of transverse section and then used for internal measurements.

outward traction the true conjugate reading is seen upon the centimeter scale on the long section and the thickness of the pubic bone upon the small section scale.

Fig. 2 shows how this instrument is adapted to the pelvic inlet. These three measurements can then be taken whenever the examining fingers are able to distinguish the promontory of the sacrum.

These inside measurements should always be taken with caution, so as not to injure the cervix nor disturb the presenting part when it is in the pelvis. Naturally if the presenting part is below the brim, it is not necessary to measure the true or diagonal conjugate.

Continuing the use of these two pieces together, the anteroposterior diameter of the outlet can be obtained as also the depth of the pubic bone. This is done by placing the curved tip upon the end of the sacrum posteriorly while the upright arm is held just beneath the pubic arch, then the centimeter measure is read off on the shaft of the long member as you face it. This gives the anteroposterior diameter of the outlet. The depth of the pubic bone can be accurately measured upon the small section, anteriorly.

To continue the outlet measurements, remove the small member and put the transverse piece upon the long section as follows:

The transverse section is held with the centimeter reading to the right, while the long section is threaded into the window of the encircling band upon the crosspiece with the curve toward the patient and the shoulder end downward.

With the patient's hips well over the end of the table so that the sacrum is readily felt at its tip and free of pressure, you are now ready to measure the transverse of the outlet and the posterior sagittal diameter.

The instrument is held by placing the thumbs in the two oval rings, thumb nails facing each other and touching the measuring points on the instrument which are fitted to the tuberosities of the ischii. This measurement is made upon the tuberosities edge and not taken from within.

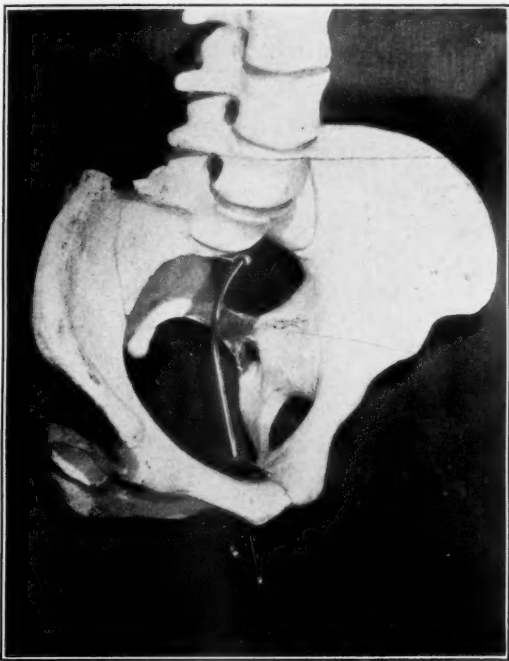


Fig. 2.—Showing use of internal pelvimeter, taking the true conjugate and thickness of pubic bone while in place. This demonstrates the curve in the long section so as to reach more fully the promontory when presenting parts, uterus or cervix, are in the way. Small ring under instrument is for traction to complete accuracy in measuring both the true conjugate and thickness of pubic bone on smaller instrument.

By proper palpation with the thumb tips going beyond and then returning, one eventually can most accurately secure this measurement, which becomes evident on the transverse bar as it is adapted to the perineum of the patient.

Next, by placing the thumb and first finger of the right hand into the cups on the transverse member and pressing firmly against the tissues to retain its position, the thumb and first finger of the left hand adjusts the curved section at its tip to the end of the sacrum, posteriorly. The posterior sagittal reading becomes evident at the lower inner edge of the window where the sections cross.

The instrument can then be removed, with readings unchanged, as the ratchets hold their adjustments (see Fig. 3). With this type of instrument, all measurement points are checked up with the finger tips and recordings are correspondingly accurate.

This instrument is of special value in funnel and generally contracted pelvis and in the accurate measurements of borderline cases, which naturally require the best judgment in their method of delivery.

Closer observation on these pelvic measurements and correct interpretation of their significance, when considering the best method of delivery to safeguard maternal and fetal life, cannot help but to improve our mortality and morbidity rate in the future.

Inasmuch as the biparietal diameter of the fetal skull is of such significance in borderline cases of pelvic contraction, I have been making biparietal notations in reference to fetal weight. In a small series of 100 cases, 93 per cent of babies weighing 6 pounds or over had a biparietal diameter of 9 cm. or more, while 84 per cent of babies under 6 pounds had a diameter averaging 8.4 cm. Only 3 babies under 6 pounds had a biparietal measurement of 9 cm. Generally speaking, bi-

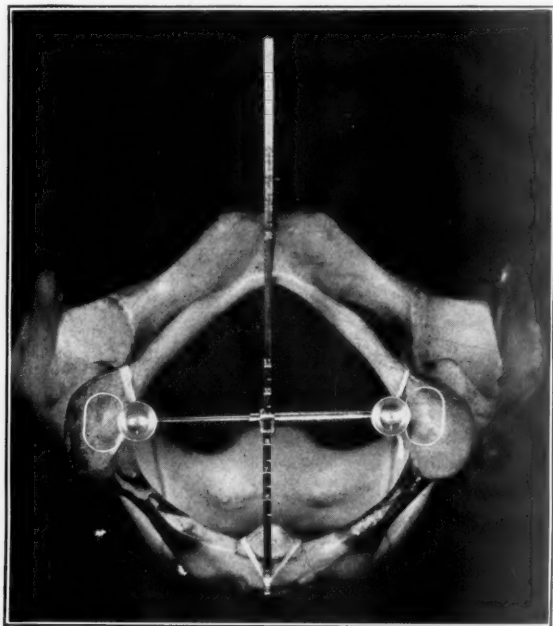


Fig. 3.—Outlet pelvimeter has been taped in place. Small internal section of instrument has been removed and transverse section threaded upon long section. Readings can be observed for both posterior sagittal and transverse outlet after instruments are removed as ratcheting keeps centimeter measure correct. Instrument made by Donald Thomas, 116 Windham Street, Syracuse, N. Y.

parietal measurements of babies at birth, weighing from 7 pounds up, did not increase with their difference of weight and were therefore usually as difficult to deliver at 7 pounds in contracted or borderline pelvis as those weighing much more. Under 6 pounds, the biparietal diameter is usually markedly reduced from 1 to 1.5 cm., making delivery of these lighter weight children more successful in moderately contracted pelvis.

Premature infants do not stand prolonged labor very well in contracted or funnel pelvis and a closer check upon the fetal heart is advisable in these cases.

The saying that small babies have large heads and large babies relatively small heads must be considered the rule, unless you can prove otherwise in the individual case.

Accuracy in pelvic mensuration becomes most important when the type of pelvis deviates from normal and the question of how to deliver to secure the best results for mother and child frequently presents a very difficult problem.

In my hands, this new pelvimeter has proved very useful, it is small, easily carried, easily read and surprisingly accurate when the anatomic points are first checked by the examining fingers.

608 EAST GENESEE STREET

## RUPTURED UTERUS: PERITONITIS, OPERATION AND RECOVERY

RALPH L. BARRETT, M.D., NEW YORK, N. Y.

*(From the Obstetric Service of the Knickerbocker Hospital)*

AT THE Woman's Hospital, in the last thirteen years, there have been twelve cases of uterine rupture associated with pregnancy or labor. Eleven of these patients had prompt laparotomy with hysterectomy or repair. All these patients recovered. One patient was treated by tamponade together with transfusion. No laparotomy was done. This patient died forty-eight hours later of peritonitis and shock.

The case which I wish to present illustrates the difficulty in making a diagnosis of uterine rupture postpartum when the lesion is of minor degree. It also illustrates the dangers to which these women are subjected if the diagnosis and treatment are delayed.

Mrs. M. H., aged thirty-one years, white, gravida iii. She had had two previous spontaneous deliveries of normal babies at term.

She was admitted to the Knickerbocker Hospital Obstetrical Service Oct. 9, 1935, in the first stage of labor, at full term. Her antepartum period had been entirely normal. Her labor in the Hospital appeared to be uneventful for about eighteen hours, contractions occurring at three- to eight-minute intervals and of moderate severity. Examination on admission indicated a vertex presentation in right occipitoposterior position with the presenting part floating and gradually settling in and fixing in the brim. Sixteen hours after admission to the hospital and about twenty-two hours after onset of labor the membranes ruptured spontaneously. She was examined by the interne at this time, who found the presenting part wedged in the brim in what he considered to be right occipitoposterior position with the cervix fully dilated. The patient continued to have strong uterine contractions for the next two hours but as there seemed to be no progress in the descent of the child, he called an attending obstetrician.

I saw the patient shortly after this, probably from two to two and one-half hours after the rupture of the membranes and the attainment of full dilatation. It was evident that there was some obstruction to delivery. Contractions of the uterus were violent and prolonged. The fetal heart was irregular, carying from 100 to 160, with considerable passage of meconium. The patient's pulse was then 112 and temperature 101°. Vaginal examination revealed a face presentation with the chin to the left and posterior. This was wedged tightly into the brim of the pelvis, and there was no advance with the uterine contractions. While the baby was large, the patient had an entirely adequate bony pelvis and, due to previous childbirth injuries, there was no obstruction from the soft parts. It was apparent that de-

livery should be accomplished as quickly as possible in the interests of both mother and baby. The patient had already had 1/6 gr. of morphine and 1/150 of scopolamine five hours previously with rectal-ether-oil four hours previously.

Under deep ether anesthesia in the delivery room, it was found that the uterus was moderately tight but would relax and the presenting part could be displaced from the brim of the pelvis. Internal podalic version seemed to be the best method of delivery. The cervix was fully dilated and fully effaced. Because of the persistent tone of the uterus even under an anesthetic, 1/2 c.c. of adrenalin chloride 1-1000 was administered intramuscularly. Following this there was prompt relaxation of the uterine musculature, allowing internal podalic version to be accomplished with comparative ease. With the version completed a nine-and-three-quarter-pound male child was slowly extracted without difficulty. The after-coming head was delivered easily and without the use of forceps. The baby showed marked asphyxiation and pallor. Respirations were established artificially. The placenta separated spontaneously at the end of five minutes and was easily expressed from the vaginal vault and cervix without unusual bleeding.

After a change of gloves the birth canal was thoroughly explored. No lacerations could be detected in the vaginal vault, cervix, lower uterine segment, or fundus. The uterus seemed to lack tone and remained large, and there was a tendency to excess bleeding. This failed to respond to the usual oxytocics administered by hypodermic. The uterus and vagina were tightly packed with iodoform gauze. All bleeding was controlled. The fundus was now easily palpable as a firm ball rising two-thirds of the way to the umbilicus. The patient's general condition was good. The blood pressure was 130/90 and pulse 90. Patient was returned to bed.

About two and one-half hours after delivery the patient was suddenly seized with sharp pain in the right upper quadrant of the abdomen which radiated upward into the right shoulder. The pulse was 100 and the blood pressure 130/80. The entire abdomen was reported to be tender. Pain was controlled by morphine. Three hours later she again required morphine for the upper abdominal and shoulder pain. The patient was vomiting and was given 1,000 c.c. of normal saline, intravenously. I saw the patient at this time. Her general condition was good, and her abdomen was somewhat tender. The pulse remained at about 100 to 110 with no drop in blood pressure. There was no bleeding. Possible undetected uterine rupture was considered, but since the bleeding had been controlled and her general condition was good, laparotomy was not done.

During the night she required several hypodermics of morphine to control pain and restlessness. The pulse increased in rate up to 150 and temperature rose to 101°. There was profuse sweating. A blood count taken early the next morning about ten hours after delivery showed hemoglobin of 66 per cent, red cells 3,150,000, white cells 17,800 and polymorphonuclears 92 per cent. The white count repeated four hours later, that is, about fourteen hours after delivery, showed white cells 28,000 and polymorphonuclears 92 per cent.

Twenty-four hours after delivery her blood pressure was 120/90. There was generalized abdominal tenderness and distention, pulse was 140 to 160, and the patient was extremely ill. She was given a clysis of 5 per cent glucose, and arrangements were made for transfusion. Four hours later after receiving the transfusion the pulse was 152, the abdomen was more distended and markedly tender, and there was persistent vomiting. The blood count at this time was, hemoglobin 95 per cent, red cells 4,650,000, white cells 23,400, and polymorphonuclears 92 per cent. At this time it was our opinion that this patient was suffering from acute peritonitis probably due to a tear through the broad ligaments or through the uterus. Her condition was very poor. We felt that our only hope would be an exploration under local anesthesia.



Upon opening the abdomen it was found to be filled with dark serous blood-stained fluid, the peritoneum was dull and glazed as was the surface of the intestines in the lower portion of the abdomen. There was no fresh blood. The uterus was firmly contracted. I felt that there must be a uterine tear to account for the blood-stained fluid and slight iodoform odor as well as the peritonitis. However, no rent was at once apparent. A careful search revealed an area, far down on the right side posterior to the right broad ligament in the lower segment of the uterus, with a small hole about 0.5 c.c. in diameter into which a knuckle of iodoform gauze protruded. Only a minute opening was present through the peritoneal surface. The fluid was quickly evacuated from the abdomen with suction, and due to the extreme condition of the patient, the operation was rapidly terminated by placing three cigaret drains, the first at the site of the small hole in the uterus, second into the right flank and the third posterior to the uterus and into the culdesac. These were all brought out through the abdominal wound, since we did not wish to disturb the uterine and vaginal packing by bringing the drains through the vaginal vault. We believed that, if necessary, at a later date such dependent drainage could be established. The abdomen was closed with through-and-through sutures. She was given a clysis following this operation and this was repeated several times in the next few days. The stomach was drained by means of a Wangenstein tube for two days, following which she was able to retain food. The bowels responded to enemas, and the uterine gauze was removed twenty-four hours after operation.

The patient had rather a stormy convalescence for the first ten days after which the functions were normal, the temperature normal, and she was discharged from the hospital on the thirtieth day after operation with the wound nearly healed. Pelvic examination at that time was entirely negative.

#### COMMENTS

I believe that this woman must bear a charmed life and that we were very fortunate in the outcome of this case. Perhaps the selection of the method of delivery was unwise. Latzko extraperitoneal cesarean section might have been chosen. The rent in the lower uterine segment was so small that it was not detected when careful examination of the birth canal was made following delivery. The sudden abdominal pain radiating to the right shoulder together with the restlessness of the patient, the high leucocyte count with high rate of polynuclear cells, even without the signs of extensive intraperitoneal hemorrhage, should have been interpreted as due to uterine rupture, and laparotomy should have been done a few hours after delivery, rather than twenty-four hours later, when a well-developed peritonitis forced the issue. Certainly the risk to the mother would have been less.

59 EAST FIFTY-FOURTH STREET

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#### Salberg and Brunet: *Trichomonas Vaginal Infestation: A Discussion of the Disease and Treatments*, Virginia M. Monthly 63: 223, 1936.

The authors state that they have tried and found unsatisfactory the following methods of treatment: (1) tincture of green soap, drying, and kaolin; (2) pyroligneous acid, boroglycerin; (3) stovarsol as a local application; and (4) silver pierate. At the present time they are using a powder consisting of oxyquiline, boric acid and talc after a thorough but gentle cleansing of the vagina, and feel that so far it has proved most satisfactory.

EUGENE S. AUER.

## ABLATIO PLACENTAE TREATED BY CESAREAN SECTION, FOLLOWED BY HYSTERECTOMY

CHARLES W. FRANK, M.D., NEW YORK, N. Y.

*(From the Obstetric Service of The Bronx Hospital)*

CESAREAN section is considered by most obstetricians the procedure of choice as the treatment for ablatio placentae. In some cases this operation must be supplemented by the removal of the uterus. Where this is done at the time of the section, because of the hemorrhagic infiltration of the uterine musculature, the dangers are not especially great. Occasionally, however, at the time of the cesarean section, the surgeon feels that the uterus is contracting satisfactorily and yet the sequellae promptly show that this is not the case. Here it requires considerable judgment and courage to subject the patient to an immediate secondary operation to save her life. This is illustrated in the case referred to below.

Mrs. H. D., aged twenty-eight, para iii, gravida iv, had had three normal spontaneous deliveries; the previous medical and surgical history was negative. She registered in the Hospital in the eighth month of pregnancy and at the time of her two prenatal visits the following notations were charted: the blood pressure was 115/70; urine negative; Wassermann and Kahn tests negative; pulse 84; fetal heart present. She had a marked exophthalmos which she said had been present since the birth of her last baby. Her basal metabolism rate was plus three.

At eight A.M., March 22, 1935, when the patient was only eight months' pregnant, she was awakened by moderately severe abdominal cramps which she attributed to an intestinal upset. These pains became progressively worse and at twelve noon the patient had a severe vaginal hemorrhage and collapsed.

She was immediately transferred to the Hospital where external examination revealed a hard, tense, rigid abdomen, with a high fundus up to the ensiform. No fetal heart could be heard or fetal parts mapped out. The patient's pulse was imperceptible and the blood pressure was 70/50, and she was in profound shock. There was a steady flow of blood from the vagina. The patient was put in the Trendelenberg position,  $\frac{1}{4}$  gr. of morphine sulphate was administered, and intravenous glucose and saline given. No vaginal or rectal examinations were made. One hour later, the patient recovered to some degree from the shock, the blood pressure had risen to 120/60, pulse 80 but very thin, and the vaginal bleeding, though diminished, was still present and continuous. The patient was typed and prepared for operation; the preoperative diagnosis was: separation of the placenta with concealed and revealed accidental bleeding.

Two hours after admission to the hospital a low classical Cesarean section was performed under general anesthesia. The uterus was blue and spotted with hemorrhagic areas, and when incised, revealed the placenta in front and completely separated, while the uterine cavity was filled with blood clots. The endometrium was irregular and shaggy.

The child, a male stillbirth, was delivered. Five millimeters of pituitrin was given intravenously and 1 c.c. of pituitrin injected directly into the uterine wall. The uterus was packed with iodoform gauze and then sutured in three layers. It contracted and remained firm and the normal color returned. The patient received a transfusion of 500 c.c. citrated blood during the operation.

Following the operation the patient's condition was found to be poor; the pulse was imperceptible; the uterus not very hard, yet not high; there was continuous bleeding from the vagina, indicating that the uterine blood sinuses were still bleeding and unchecked by the uterine packing or pituitrin. A second transfusion of 350 c.c. of blood was given by the Soresi direct method one hour after the first, and one hour later, still a third transfusion was given of 500 c.c. of whole blood. Meanwhile, a packing of ten yards of iodoform gauze was tightly packed into the vagina and against the uterus, but within a short time bleeding again appeared at the vagina.

Consultation at this time decided that, although hysterectomy was the only procedure, the patient's condition was so critical as to preclude any further operation. Accordingly, the patient was left alone, supportive treatments being given meanwhile in the form of hypodermic stimulation, saline infusions, and bandaging of the extremities. At 8:35 that evening, six hours after the cesarean section, the patient was still alive but her condition was unchanged, pulse was imperceptible, blood pressure exceedingly low, and vaginal bleeding present and persistent. It was decided to operate again. Accordingly, under light gas and ether anesthesia the incision was reopened, the uterus delivered into the open wound and amputated supravaginally. At the same time, a transfusion of 600 c.c. of whole blood was started. The abdomen was closed with through-and-through silk sutures, the vaginal packing removed, and the patient put to bed. Clysis was maintained thereafter for the next twenty-four hours. Her condition remained critical for several days, but the pulse improved and there was no further bleeding.

During the next few weeks the patient steadily improved as to pulse, blood pressure, and general condition. Her temperature dropped from 102° to 100° on the third day and never went up beyond that during her entire stay in the hospital. The hemoglobin rose from 43 per cent on the third day after operative to 71 per cent shortly before discharge from the institution. The abdominal incision healed by primary intention and without any complications. About a week after the operation, the patient complained of soreness in the right lower abdomen and numbness and coldness of the entire right lower extremity. Shortly after there appeared a small area of superficial gangrene on the outer one-third of the right middle thigh and also on the heel. These necrotic areas became definite ulcers about the size of a quarter and were treated by means of cold quartz therapy, and cleared up in about two weeks. On April 24, a little more than one month after admission, the patient was discharged from the hospital and transferred to the clinic for baking and massage treatments to the right lower extremity.

This case presents the following interesting points: First, the patient survived two grave operations. At the time of the cesarean operation she was in shock and remained that way for at least eight or nine hours. Second, she was almost exsanguinated at the time of the second operation; although 1,350 c.c. of blood as well as 2,000 c.c. of saline were given, this flowed out of her vagina almost as rapidly as it was administered. So extreme was her condition that it was felt that the slightest operative procedure would precipitate a fatal issue. The cause for the continued bleeding is problematic; at no time either before or after the delivery were there any signs of toxemia or other predisposing causes for hemorrhage. There was nothing wrong with her blood pressure or urine at any time. Both Wassermann and Kahn tests were negative for syphilis. There was nothing apparent in the uterus either during the first or second operations, or in the gross or microscopic appearance that would account for the persistent bleeding. There were no signs of a fibroid or other pathologic condition in the uterine muscle. The uterus itself reacted very well to pituitrin; it remained fairly firm and contracted, but still the sinuses were open and kept bleeding. The exophthalmos which

was observed in the clinic gave rise to a diagnosis of possible hyperthyroidism, but her pulse was only 84 and her basal metabolism rate was only plus-three. The peripheral neuritis of the right lower extremity may have been due to an impaired peripheral circulation, possibly the result of bandaging the extremities and thus shutting off the blood supply.

1882 GRAND CONCOURSE

## PREGNANCY IN A PATIENT SUFFERING WITH SCLERODERMA

EULA ENO, A.B., M.D., DES MOINES, IOWA

*(From the Service of the Margaret Williamson Hospital, Shanghai, China)*

THE patient, a Chinese woman, aged thirty-one years, was admitted to the hospital on Jan. 30, 1933, at the end of her first pregnancy. She had been in labor for nearly forty-eight hours, and her membranes had ruptured twenty-four hours before admission. She had been treated by a midwife, who had torn or cut the perineum and vagina in several places.

General physical examination at the time of admission revealed a patient with a curious masklike facial expression. She had a more or less generally distributed edema, more severe over legs, thighs, lower abdomen, and vulva. The consistency of the edematous areas was much firmer than that of the ordinary edema of toxemia. Her knee joints were stiff, her legs fixed in extension, and her elbows were also stiff, with forearms fixed at about midflexion on the arms. The wrist joints were ankylosed, as were her hands, with fingers slightly flexed on the palm. Muscular wasting seemed limited in the main to the forearms. Her pulse was 110, her temperature normal, and her blood pressure 150/110.

Laboratory findings were as follows: Urine contained heavy albumin, and many granular casts. Blood examination showed hemoglobin 65 per cent; erythrocytes 3,500,000; and leucocytes 16,600, with 89 per cent polymorphonuclears.

Obstetric examination gave negative findings in pelvimetry, except that the Baudeloque was a little short, 18 cm. The abdomen was enlarged to the size of a full-term pregnancy, with the abdominal wall so firm as to preclude accurate palpation. Just above the symphysis, there was some pitting edema, but the fundus area of the uterus was almost boardlike in consistency. The sensation was much the same as that of her legs, thighs, and face. No relaxation of the uterus could be made out, and no fetal heart sounds were found. Rectal examination was unsatisfactory because of the edema of the vulva. Vaginal examination showed the cervix stiff, canal not wholly obliterated, and dilatation of 7 cm. Foul, meconium-stained amniotic fluid was escaping, and the fetal head was very high with the bi-parietal diameter above the inlet of the pelvis.

Differentiation or adjudication as to the relative influences of various factors was almost impossible. There was an obvious toxemia, with its edema; there might well be a tetanic uterus in view of the long labor; and there was the underlying scleroderma. The patient needed to be delivered and the most conservative available method seemed to be craniotomy. This had to be followed by embryotomy. The operation was very difficult, because the legs could not be bent on the thighs, and were held apart by nurses. In addition, the edema of both vulva and thighs made the outlet small and difficult of access. The child was a medium-sized female, and it is interesting to note that the extremities, particularly the lower, exhibited much

the same subcutaneous woody sensation and adherence of skin to lower layers as that of the mother's body. Both of the child's feet were in the attitude of talipes varus, and the ankle joints were absolutely immobile.

The puerperium was comparatively uneventful, patient having fever as high as  $101^{\circ}$  daily until the fifth day, after which she was afebrile. Her blood pressure dropped rapidly, and by the fifth day was 112/60. Her urine was negative by that time, also. The edema disappeared, leaving the sclerodermic portions of her body unchanged. Her perineal and vaginal wounds healed badly, and she had very bad support on discharge.

One year and nine months later, the patient was again admitted, pregnant, at term, and in labor. She had had little if any midwife manipulation this time, and the fetus was alive in utero. Physical examination showed the same masklike facies, and the same condition of extremities as before. There was no evidence of superadded edema, and the abdomen was distinctly softer than on the first admission. Rhythmic contractions of the uterus were easily palpated. Blood pressure was 114/80, urine negative, and general condition good.

Delivery was by classical cesarean section. It was followed by supravaginal hysterectomy, because of the question of potential infection from manipulation before admission. The child, a female, was normal, and weighed 2,525 gm. The postoperative course was uneventful, with a slight elevation of temperature the first four days, without symptoms. The wound healed by first intention, and the patient went home on the twentieth day. A section of the abdominal wall taken at the time of operation is pathologically reported as showing "a definite increase in fibrous and connective tissue, subcutaneously."

The baby was on mixed feeding while in the hospital, and was discharged weighing 350 gm. more than at birth. She was breast fed at home, and was in good condition at eight months. She has since died of measles.

There is no history obtainable concerning the development of the condition, except that the patient herself says she has been as stiff as she now is since the age of eight. She believes the beginning of the stiffness dates from a fall which she had at that time. The sequence of events is almost certainly just the reverse, of course. The patient does not believe that there is any increase in the severity of the condition at present, and certainly there has been no appreciable change in the three years she has been under our observation.

There is such confusion among students as to the etiology and pathogenesis of scleroderma that no attempt is made here to discuss it. Multiple involvement or dysfunction of endocrine glands is the etiologic factor most often mentioned. Evidence of such dysfunction seems lacking in this patient. She has neither the mental sluggishness of a myxedematous individual, nor any of the nervous manifestations of Graves' disease. She is intelligent, active, and alert. Her menstrual history before marriage was negative, and she became pregnant two months after her marriage.

The case is reported mainly from the point of view of interest, and not because it is felt that the report in this form can make any scientific contribution to the subject of scleroderma in general.



## BRENNER'S TUMOR

A. M. GNASSI, M.D., JERSEY CITY, N. J.

*(From the Pathological Department, Jersey City Medical Center)*

THE unusually few cases of Brenner's tumor reported is due, in our belief, not only to an infrequency of occurrence but to a lesser extent, to the still esoteric features of the neoplasm. With this in mind we are reporting a case of solid cell Brenner's tumor.

Mrs. R. A., aged forty, was admitted to the Jersey City Medical Center, Aug. 28, 1935, complaining of a profuse vaginal bleeding of twelve days' duration. The family history was irrelevant. Her past history included a cholecystectomy three years before admission, and in the following year a right salpingo-oophorectomy and an appendectomy of which we were unable to obtain any information or record. She had been married twenty-one years and had three children, now living and well, who were delivered with normal parturition and postpartum courses. Menstruation began at the age of fourteen years, occurring every twenty-eight days and lasting three days. August 16, one week after a normal menstrual period, bleeding began and had continued until admission.

The general physical examination, with the exception of tenderness in the left lower quadrant, was essentially negative. Pelvic examination revealed a lacerated lobulated cervix with good pelvic support, a smooth elongated uterus freely movable and a small tender mass in the left fornix. The temperature was normal and the blood pressure was 112/80. The laboratory data noted a red blood cell count of 3,800,000 with a 70 per cent hemoglobin, Tallqvist, a white cell count of 8,200 with a differential count of 70 per cent polymorphonuclear leucocytes, 28 per cent lymphocytes, and 2 per cent large monocytes, eighteen minutes for sedimentation time, a negative Wassermann, and occasional red blood cells and a few epithelial cells in the urine.

On August 29, under spinal anesthesia, a supravaginal hysterectomy and a left salpingo-oophorectomy were performed. The right adnexa were not present. The right round ligament was firm and firmly attached to the anterior surface of the uterus which was enlarged, firm, and smooth. The left tube and ovary were densely adherent and fixed in the culdesac with numerous adhesions.

The postoperative course was uneventful and the patient was discharged Sept. 9, 1935. At the present time, she is well.

Pathologic examination revealed a uterus which measured 7 by 6 by 6 cm. The surfaces were smooth with the exception of the superior which was slightly roughened. On section, the wall attained a thickness of 1 cm. The endometrium was slightly raised and covered with a sanguineous material. The tube was roughened, thickened and adherent to the ovary. Microscopically, subacute endometritis, fibrosis of the uterus and chronic salpingitis were evident.

The ovary measured 3 by 2.3 by 1.8 cm. The peritoneal surfaces were smooth and lobulated with the exception of a roughened area which gave attachment to the tube. On section, the cut surfaces presented a roughly spheroidal, sharply defined, firm, grayish white nodular mass measuring 1.6 cm. in its largest diameter. This mass was eccentrically placed and at the hilum was surrounded by 0.1 cm. of ovarian stroma which gradually increased to attain the thickness of 0.6 cm. at the

opposite pole. Within the ovarian stroma there were one lutein and several thin-walled cysts. Microscopic examination revealed an ovarian stroma supporting a

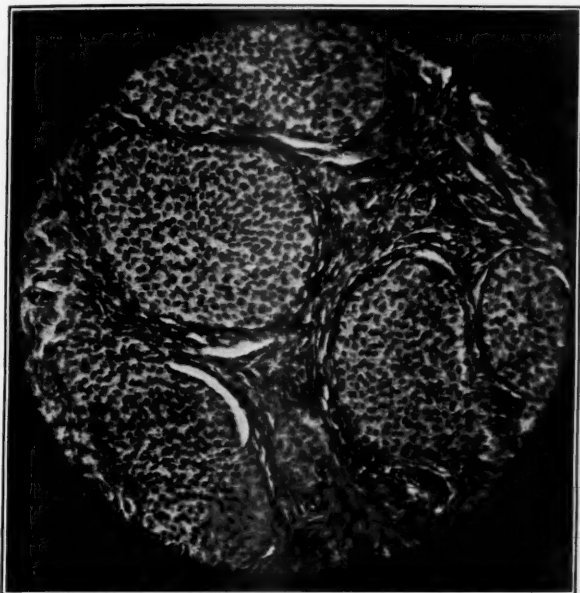


Fig. 1.—Low power magnification showing radiating groups of epithelial nests.

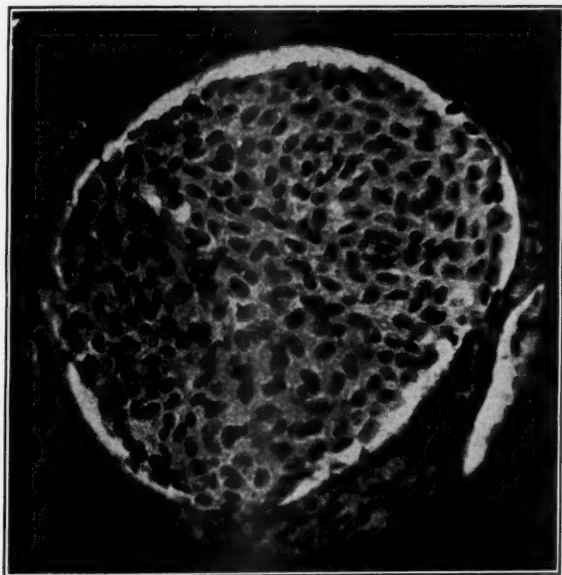


Fig. 2.—High power magnification of Fig. 1.

lutein and several follicular cysts. The tumor was well demarcated from the ovarian stroma by partially hyalinized, slightly acidophilic, elongated or oval-shaped cells, having a parallel arrangement. As the stroma dips down between the epithelial

nodules its arrangement closely resembles that of the interstitial lamellae as seen in compact bone. Surrounding the epithelial nests, the partially hyalinized fibrous tissue assumes a concentric arrangement to form narrow bands attaining a thickness of three or four cell layers. The epithelial nests are composed of groups of oval cells radiating to the periphery where they are limited by a single layer of fusiform or spindle-shaped epithelium parallel to the fibrous capsules. Their nuclei are oval or round, vesicular and dotted with a fine chromatin network. The cytoplasm is a delicately granular structure and only slightly acidophilic. The pericellular membranes are fairly well defined. Small round or oval vacuoles of the cytoplasm are often seen. The peripheral cells are conspicuous, for their smaller nuclei are comparatively rich in chromatin. The vascularity is poor. Mitotic figures are extremely infrequent.

#### CONCLUSIONS

1. The gross and microscopic findings are typical and the tumor is not to be confused with granulosa cell or epidermoid carcinoma.
2. The histogenesis is somewhat obscure but possibly related to the serous cystoma (Meyers).
3. The tumor is of a very low degree of malignancy, and once removed, the prognosis is usually good.
4. Better clinical and microscopic data should increase the number of cases on record.

I wish to thank Dr. J. M. Rector for allowing me to abstract the case and Dr. J. Goldstein for his valuable advice.

### ACCIDENTAL RUPTURE AND SUCCESSFUL LIGATION OF AN UMBILICAL ARTERY BEFORE ONSET OF LABOR

ERNEST W. PAGE, M.D., LOS ANGELES, CALIF.

*(From the Department of Obstetrics and Gynecology, University of Southern California, and the Los Angeles County Hospital)*

MRS. C. B., aged thirty-five, entered the Los Angeles County Hospital at 1:30 P.M., Nov. 16, 1935, with the complaint of vaginal bleeding for five days.

The past history was not essential. She had had five full-term pregnancies, and two spontaneous abortions. The fifth pregnancy was complicated by polyhydramnion and stillbirth. Her largest baby weighed nine pounds and was delivered spontaneously.

The patient was due on November 13, and her pregnancy had been entirely uneventful until five days before admission, when she began to have slight vaginal bleeding, without pain. On the morning of entry, she passed two large clots, but at no time had the bleeding been excessive.

Physical examination revealed a moderately obese female appearing to be in good general condition, and showing no evidence of anemia. The findings were entirely negative except for slight pretibial edema and a blood pressure of 138/84. There were no uterine contractions and no vaginal bleeding on entry. All pelvic measurements were normal. The height of the fundus was 32 cm., fetus lying in L.O.A. position, fetal heart tones 148. Urine negative. Hemoglobin 70 per cent; R.B.C. 4,160,000; W.B.C. 11,000; 80 per cent polys. Wassermann negative.

In accordance with our usual procedures in cases of suspected placenta previa, no rectal examinations were done, but at 4 P.M. (after obtaining a suitable donor for

transfusion, if needed) a sterile vaginal examination was made. The cervix was found to be 50 per cent effaced, 2 cm. dilated, and fetal head floating in L.O.A. position. Placental tissue was felt at the margin of the internal os, confirming the diagnosis of placenta previa marginalis.

About 30 to 40 c.c. of blood were lost during the examination, and it was decided to rupture the membranes. A long hemostat was introduced through the cervix, the membranes grasped, and the instrument withdrawn. Unfortunately, there was a forelying cord which had not been recognized by the examining finger, and the loop of cord was withdrawn in the grasp of the hemostat. At the point of injury to the cord, dark blood spurted for a considerable distance with each pulsation. The bleeding point was ligated with a plain catgut suture and hemostasis secured. The cord was then replaced with some difficulty through the cervix, and a full dilatation (No. 5 Voorhees) bag was inserted and filled. Immediately after the insertion of the bag, the fetal heart tones became weak and irregular, rate 60; but by external manipulation, pressure was apparently removed, and the heart tones became regular, rate 150. The patient was returned to bed, and a two-pound weight was attached to the bag.

Active labor began at 7 P.M. (three hours after insertion of bag), and at 10 P.M., the cervix was 6 cm. dilated, 80 per cent effaced, with uterine contractions occurring every three minutes, moderate in intensity. Throughout labor, the fetal heart tones remained at the rate of 150. She was given  $7\frac{1}{2}$  gr. of nembutal and  $\frac{1}{150}$  gr. of scopolamine, and prepared for delivery. At 10:40 P.M., the bag slipped through the cervix, was deflated, and removed. Under complete anesthesia, a 6 pound 12 ounce male infant was delivered easily by version and extraction. The cervix and uterus were explored and found intact. The placenta was removed manually and the uterus packed with 8 yards of 8-ply gauze. Total measured blood loss was 350 c.c. The infant cried spontaneously and vigorously, showed no cyanosis, gained well, and left the hospital in good condition. Puerperium was normal, the highest temperature recorded was 99°, and the mother was discharged on November 27.

The umbilical cord measured 50 cm. in length and was attached centrally to the placenta. The latter appeared normal except for slight maceration at the periphery. One umbilical artery was ligated 30 cm. from the placenta. The umbilical arteries were probed and perfused with water. There was an apparent obstruction of one umbilical artery at the site of the ligature. This was confirmed by microscopic section taken through the suture, which was seen to pass around the artery. There was some effusion of blood into the substance of the cord, but otherwise it appeared histologically normal.

#### COMMENT

Complete rupture of an umbilical cord is fairly common, since over 700 cases are mentioned in the literature, whereas isolated rupture of one or more umbilical vessels is extremely rare. Forssell,<sup>1</sup> in 1908, classified the tearing of single cord vessels into three groups: (A) Rupture of a varix of the umbilical vein (eight case reports quoted); (B) rupture of a vessel with velamentous insertion (fairly common); and (C) the tearing of single cord vessels. In this last group, four writers have reported ruptures of the umbilical vein; Hamill,<sup>2</sup> Keller,<sup>3</sup> Sackett,<sup>4</sup> and Pahl.<sup>5</sup> Injuries to one or both umbilical arteries have been reported by Wiere,<sup>6</sup> Westphalen,<sup>7</sup> Lonne,<sup>8</sup> and Siddall.<sup>9</sup> All of these last cases occurred during the delivery and were due to tearing injuries, two of the four accidents resulting in death of the fetus. In none of the cases reported was such an injury recognized prior to delivery, and there is apparently no recorded report of a living baby obtained following rupture of a cord vessel prior to labor, nor of an attempted ligation of a ruptured vessel.

It is interesting to speculate on the effect of occluding one umbilical artery in utero. Evidently, through arterial anastomoses or increased flow through the re-

maintaining artery, there is no deficiency in oxygenation of the fetal blood, since no asphyxia was noted in this case, and the fetal heart tones, once established after replacement of the cord, showed little variation in rate, rhythm, or quality. The case presented demonstrates the feasibility of ligating a bleeding vessel should such an accident occur.

Acknowledgment is made to Dr. E. M. Lazard and to Dr. Lyle G. McNeile for permission to report this case.

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### HEMATOMETRA DUE TO ATRESIA OF THE CERVIX FOLLOWING CAUTERIZATION

A. L. HENKIN, M.D., BROOKLYN, N. Y.

**C**AUTERY treatment of chronic inflammatory lesions of the cervix is universally adopted at the present time; however, it is not without danger, and the purpose of this report is to call attention to this fact. The fact that great care must be used in the application of this modality was emphasized by others.

The case herewith reported is that of Mrs. J. A., aged twenty-two years, para i, grav. i, whose menstrual history was regular every month, moderate flow, and five days' duration with no pain. In April, 1936, she had a cauterization of the cervix for vaginal discharge and pain in the right lower abdomen. Following this treatment she did not menstruate in May and June; and because of pain and amenorrhea she was readmitted to the hospital where some operative procedure was performed, and she was kept in the hospital for three weeks. After her discharge she again failed to menstruate for two months. In August she was again admitted to the hospital for a dilatation of the cervix, which was followed by some bloody discharge. In spite of that she did not menstruate; so in October she was admitted to the hospital again for dilatation; but the patient was not relieved. At the expected time of her menstruation she complained of pain for three days, but there was no vaginal flow. On November 10 the patient was seen by me; her chief complaints were amenorrhea and pain in lower abdomen. Except for secondary anemia her general condition was negative. The local condition disclosed a multiparous perineum, absence of vaginal portio of the cervix; uterus the size of a three months' pregnancy with a mass in the right fornix the size of an orange. Speculum examination disclosed again an absence of the cervix except for a small dimple in the vault, where a small pinkish area of columnar epithelium was left.

A diagnosis of hematometra and hematocolpos due to destruction of the vaginal portio of the cervix by cautery was made.

**Operation.**—A tenaculum was applied to the vault of the vagina where the cervix was supposed to be; an incision was made in the anterior vaginal vault extending from a point one inch below the meatus down to the tenaculum; the vaginal wall was dissected laterally; the bladder was identified and retracted upward exposing what was left of the cervix. An incision was made into the cervical tissue which was



followed by a gush of black, thick tarry material. The finger was inserted into the cavity which had a closed pouch at the lower end which was bulging toward the rectum; while the upper end was surrounded by a ring of almost cartilaginous tissue which did not admit the tip of the little finger and from which the tarry material continued to escape; the vaginal mucous membrane of each side were then sutured with chromic sutures to the cervical mucous membrane on the corresponding side, thus forming a canal about an inch long which was open anteriorly. The patient had an uneventful recovery. Examination four months later disclosed a normal-sized uterus with patent canal which allowed free passage of a uterine sound.

The experience gained from the report of this case and to be emphasized is:

1. Whenever cautery is used in the treatment of chronic cervical diseases, the patient is to be kept under observation to prevent stenosis or complete atresia,
2. The indiscriminate use of cautery in the treatment of the cervix is not without danger.

It seems to me also that no cautery should be used in the presence of acute inflammatory lesions. A case of death following cautery of the cervix for endocervicitis in presence of acute infection is known to the author, but because of incomplete facts in the history it cannot be reported at present.

707 WILLOUGHBY AVENUE

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## TUBERCULOSIS OF THE BARTHOLINIAN GLAND

J. HERSH, M.D., PITTSBURGH, PA.

**T**UBERCULOSIS of the bartholinian gland is a rare infection as shown by the scant reports of this pathologic entity in the literature. I am reporting a case complicated by an anal fistula also tuberculous and cured by excision of the bartholinian gland and fistula by a two-stage surgical procedure.

### CASE REPORT

Miss L. B., a white woman aged thirty-two years, was seen March 28, 1935, with a history of having developed a painful swelling on the right side of her vagina four and one-half years ago. The gland was incised, drained, and two years later the swelling returned, necessitating a second incision and drainage by her family physician. An opening persisted on the right side midway between her vagina and rectum and has been discharging continuously since the last operation.

Her past history revealed a boil on the right side of her rectum eight and one-half years ago which was incised and continued to drain for four months before complete healing took place.

Four years ago she suffered a "nervous breakdown."

The general physical examination was essentially negative. The examination of the external genitalia revealed a hard, firm right bartholinian gland the size of a hazelnut from whose duct no discharge could be expressed. In the right ischio-rectal space about 2 cm. to the right and slightly above the anus was a fistulous opening, the size of a match head, from which could be expressed, both on pressure over the right bartholinian gland and on the perineum, a thick mucoid discharge. Probing of the sinus revealed extension upward but not into the right bartholinian gland and downward and backward toward the rectum above the anal sphincter.

Vaginal examination revealed a nulliparous cervix with an erosion the size of a dime. Bimanual examination was negative. A diagnosis of chronic bartholinitis, cervical erosion, and anal fistula was made and operation was advised.

The laboratory examination revealed nothing of note, the Wassermann and Kahn tests being negative, and the blood count and urinalysis within normal limits.

The patient was admitted to the Passavant Hospital and operation was carried out Apr. 8, 1935, under ether anesthesia. A bimanual examination revealed no abnormalities in the pelvis. The cervix was cauterized and then a solution of methylene blue was injected into the fistulous opening which immediately escaped from the anus. The right bartholinian gland was exposed by an incision external to the labium minus, the dissection being carried out from the lateral aspect of the gland toward the duct. As the gland was being dissected and drawn out of its bed inward toward the duct, the upper limit of the fistulous tract became visible, some of the dye having stained the lateral inferior pole of the gland.

The entire fistulous tract was then laid open and completely dissected out, beginning at the lateral inferior aspect of the right bartholinian gland going downward and outward to the external opening and then inward and backward to the pectinate line in the right upper quadrant of the rectum where the tract was amputated, leaving the internal fistulous opening.

Because of the extensive tissue removal extending from the vagina to the right ischiorectal space and rectum, it was thought advisable to leave the severance of the sphincter muscle until the wound had granulated in enough laterally and under the sphincter muscle to prevent retraction of the sphincter ends.

A double strand of black silk was guided into the internal opening of the fistula and tied about the sphincter muscle. The wound was packed with iodoform gauze, several loosely placed silkworm-gut sutures were inserted in the lateral margins of the wound, and the patient was returned to bed.

The packing was removed on the fourth day and the wound was loosely repacked. This procedure was repeated every third day, thus allowing the wound to granulate in from the bottom. On May 28, 1935, the wound had completely granulated in, there remaining only a small sinus, the bed of the silk ligature which formed a simple straight fistula. There was enough granulation tissue present about the sphincter muscle to prevent any retraction of the muscle ends should they now be severed and thus under direct infiltration anesthesia with 1 per cent novocaine solution, a grooved director was inserted into the internal opening, the tract laid open from above downward, the black silk "seton" removed, and the tract gently curetted. The sphincter ends barely separated with this incision and the patient was discharged from the hospital at the end of forty-eight hours. On June 21, 1935, the sphincter control was perfect and the wound healed.

The pathologic diagnosis submitted by Dr. R. C. Hamilton, Pathologist to the Passavant Hospital, was as follows: Ischiorectal fistula (tuberculous); miliary tuberculosis of Bartholin's gland; chronic bartholinitis.

With the diagnosis of tuberculosis of both the bartholinian gland and the anal fistula revealed, a roentgenogram was taken of the patient's chest on June 20, 1935, but showed no evidence of a tuberculous process, either old or recent.

445 UNION TRUST BUILDING

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Williams, E. Ulysses: Ante-Natal Diagnosis of Quadruplets, *Brit. M. J.* 2: 1206, 1935.

The diagnosis of twins or triplets by x-ray after the sixth month of pregnancy is common, that of quadruplets less so. The author presents a case of quadruplets diagnosed at thirty weeks, and report is accompanied by plate. In the literature only one other instance of such diagnosis is found, that in Manchester in 1934.

F. L. ADAIR AND S. A. PEARL.

## THE TREATMENT OF GONORRHEAL VAGINITIS WITH GONOCOCCUS FILTRATE

A. J. WHITEHOUSE, M.D., LEXINGTON, KY.

A MULTIPLICITY of methods and results reported for the treatment of any condition is usually indicative of the inadequacy of the procedure in use at the time. Consequent to a discussion of the unsatisfactory results of local treatment in cases of gonorrheal vaginitis in the Children's Clinic, the matter was taken up in the Gynecological Section of the Venereal Disease Clinic.

The lack of uniformity of results and the disadvantages of the use of the ovarian follicular hormone led to the search for some other more constant method and one amenable to the economic limitations and conditions of a Public Health Clinic. Many of the patients under treatment are children of mothers in the Venereal Clinic. Needless to say, the usual difficulties attendant upon a City Venereal Disease Clinic along lines of continuity of treatment and follow-up were encountered. Also, the premise on which the use of the ovarian follicular hormone has been based (the desquamation of an infected membrane) would seem not to comprehend the possible presence of some cervical glands, especially in those cases near puberty, and their infection by the gonococcus. Because bactericides do not reach the well-established infection hidden in the tissues, the production of immunity would seem to be the desired objective of research. However, the production of immunity to gonorrhea is more delicate and less stable than that to other infections. Corbus found that gonococcus filtrate or toxin prepared from a special medium, when injected intradermally, was capable of stimulating the body to the production of gonococcus antibodies. The willingness of the manufacturers of Corbus-Ferry gonococcus filtrate to furnish some of this material in the treatment of these cases led to its trial.

This report includes 30 children of whom: 5 patients refractory to the filtrate are receiving other treatment; 13 stopped before receiving adequate treatment; and

PATIENT	COLOR	SEX	AGE	25 PER CENT SOL.	DOSE	2.5 PER CENT SOL.	DOSE	LABORATORY	DISPOSITION
				c.c.		c.c.			
J. B.	C	F	12	0.05		0.05-1.0	(23 inj.)	Suspici.	Clinical cure
V. G.	W	F	10	0.05-0.55	(11)	0.05-0.55	(12 inj.)	Neg.	Discharged
B. H.	W	F	8	0.05-0.5	(10)	0.05-0.8	(13 inj.)	Neg.	Discharged
C. H.	W	F	6	0.05-0.5	(10)	0.05-0.8	(13 inj.)	Neg.	Discharged
B. J. H.	W	F	9			0.05-0.5	( 9 inj.)	Neg.	Discharged
G. J.	W	F	7			0.05-0.3	( 6 inj.)	Neg.	Discharged
V. J.	W	F	7	0.05-0.15	( 3)	0.05-1.0	(22 inj.)	Neg.	Discharged
M. B. L.	W	F	9	0.05-0.7	(14)	0.05-1.0	(23 inj.)	Neg.	Discharged
M. L. M.	W	F	5	0.05-0.5	(11)	0.05-1.0	( 8 inj.)	Neg.	Discharged
M. L. M.	C	F	6			0.05-0.4	( 7 inj.)	Neg.	Discharged
A. M.	C	F	6			0.05-0.3	( 6 inj.)	Neg.	Discharged
G. W. W.	W	F	7			0.05-0.3	( 6 inj.)	Neg.	Discharged

5 cases being carried on.

13 stopped before adequate treatment.

12 were discharged with clinical cure and absence of bacteriologic evidence of gonococcal infection. After using a 25 per cent dilution of the filtrate once a week for a short time, it was thought wise to use a greater dilution more frequently, and the patients were given increasing doses of a 2.5 per cent solution of the filtrate twice a week. The table covers the principal facts. There were only two reactions; maximum temperature 101° F. and general malaise of about six hours' duration. One patient was discharged with persistent extracellular gram-negative diplococci, but apparent clinical cure.

These results are reported merely for purposes of comparison with those of other methods in the search for a satisfactory treatment of this condition. The approximately 70 per cent of good results is much better than that obtained previously in the Children's Clinic with local treatment.

164 MARKET STREET

### EPIDEMIC PAROTITIS IN LATE PREGNANCY\*

R. S. SIDDALL, M.D., DETROIT, MICH.

(From the Department of Obstetrics and Gynecology, Harper Hospital)

JUDGING from the literature, mumps in the latter part of pregnancy is a very rare occurrence. When the complication was diagnosed in the case outlined below, consultation of several textbooks on obstetrics (Williams, DeLee, and Curtis) yielded no information whatsoever as to the prognosis or treatment. Only two relevant case reports were found in a rather thorough search through the periodic literature of the last twenty years. In 1931 Moore<sup>1</sup> described a severe manifestation of the disease about two months before term in the second pregnancy of a woman who already had a serious cardiac condition. The patient recovered after a hazardous illness but was delivered a month later of a stillborn macerated fetus. Recently, Dutta<sup>2</sup> of India reported the death of a primigravida at the eighth month who became affected during an epidemic of mumps among the native troops. She developed acute glomerular nephritis on the fifth day, was delivered of a stillborn fetus on the eighth, and died of the nephritis on the eleventh day. In addition to these two instances there was occasional mention of other cases, including one with transmission of the disease to the fetus in utero (Greenhill<sup>3</sup>), but no definite case reports or references were found. Two of Sinnecker's<sup>4</sup> cases were possibly instances of epidemic parotitis occurring postpartum.

Mrs. J. A. D., thirty-one years old, primigravida. The last menstrual period occurred on July 25, 1935 from which the expected date of confinement was estimated for May 1, 1936. There was the history of pneumonia at nine years. Two years later (1917) she had had a tonsillectomy, adenoidectomy, and submucous resection of the nasal septum. Appendectomy was performed in 1922. In 1929 there had been a suspicion of pulmonary tuberculosis, but roentgen ray examinations at that time and again in January, 1935 were negative. In 1933 the patient had a severe attack of scarlet fever which, however, left no permanent kidney involvement. The general physical and obstetric examination showed nothing noteworthy, except some suppression of the breath sounds over the lower right side of the chest posteriorly, which was thought to be due to thickened pleura from pneumonia.

Except for moderate nausea and vomiting in the early months, the pregnancy was essentially uneventful until three weeks before the expected date of delivery. She was seen on April 9, 1936 because of swelling on the right side of the neck and

\*Presented before the Detroit Obstetrical and Gynecological Society, December 1, 1936.

face. This had been preceded by several days of general malaise. The temperature was 99.6° F. Behind the angle of the jaw on the right and pushing up the lobe of the ear was a soft, doughy swelling which extended upward in front of the ear and forward over the masseter muscle. There was also puffiness below the left ear. The throat was slightly injected, and the orifices of both Stenson's ducts were swollen and reddened. By the next day the swelling had greatly increased on both sides, giving a typical picture of epidemic parotitis. There was no history of exposure, though the patient stated definitely that she had never had mumps. Treatment consisted of bed rest and analgesics for pain and stiffness of the jaws. The patient, a graduate nurse, made frequent readings of her temperature which never went above 100° F. Swelling began to subside on the fifth day and had entirely disappeared by the twelfth.

On May 13, 1936, after a labor of twelve hours induced by castor oil and quinine, the patient was delivered spontaneously of a male child weighing seven and one-fourth pounds and appearing normal in every respect. The puerperium was afebrile and normal, and the child gained satisfactorily on breast feeding supplemented by evaporated milk formula.

This case is of interest for two reasons:

1. Because of the apparent rarity of epidemic parotitis complicating pregnancy. This is the only case to occur among the 5,000 to 6,000 private and clinic obstetric patients whose clinical course has been known to me. Greenhill<sup>3</sup> stated that there had been only one such instance at the Chicago Lying-In Hospital in 35,000 deliveries.

2. Notwithstanding the prognosis obtained from the few reports in the literature, the disease ran a mild course and caused no difficulty. It seems possible that only severe cases have found their way into the literature and that there are many others of such slight gravity as to appear unworthy of comment.

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955 FISHER BUILDING

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Dodds, Gladys H.: The Visscher-Bowman Test for Pregnancy, Brit. M. J. 2: 224, 1936.

Visscher and Bowman described the following chemical test for which they claim great accuracy: To 1 c.c. of urine are added one drop of 1 per cent hydrogen peroxide, five drops of a 1 per cent phenylhydrazine hydrochloride solution in water, five drops of a 5 per cent methyl cyanide solution in water and 5 drops of a concentrated hydrochloric acid. The mixture is heated in a water-bath for twenty-five minutes.

A russet color and thick flocculent precipitate denotes a strongly positive reaction; a dark brown and slightly flocculent precipitate shows a weakly positive result. A brown color and slight powdery precipitate shows a doubtful negative result, and no color change with no precipitate denotes a negative test.

The author investigated 100 pregnant patients and obtained correct results in 90 per cent of cases. In nonpregnant women the test was correct in 88.8 per cent. The percentage of error among the nonpregnant group is too high to make the test of any real value.

F. L. ADAIR AND S. A. PEARL.



## PREGNANCY AND NEPHRECTOMY

W. G. CUMMINGS, M.D., WINNETKA, ILL.

*(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and the Evanston Hospital.)*

THE case herewith reported is that of a nephrectomy during the first month of gestation, the latter being undiagnosed, which was followed by a normal pregnancy, labor, and puerperium.

Mrs. A., a twenty-four-year-old white woman, first seen by me on March 15, 1935, at which time she complained of nausea of ten days' duration and pain in the right kidney area, which had been present at intervals since 1932. She thought she might be pregnant. The last normal menstrual period was March 4, 1935. Menses had always been regular and normal.

In 1932, she delivered a six and one-half months' macerated stillbirth, at which time she had pus in the urine and hypertension. This had never been treated. She had had no other pregnancies, and the rest of her history was essentially negative.

Physical examination was negative except for tenderness in the right costovertebral angle and large amounts of pus cells in the urine. Blood pressure was 110 systolic and 70 diastolic. I could find no evidence of pregnancy at this time.

She was referred to the Department of Urology at the Evanston Hospital for diagnosis and treatment. She entered the hospital March 28, 1935. A cystoscopic examination was made by Dr. James Farrell who made a diagnosis of right ureteral calculus and right pyonephrosis. The urine showed a 3-plus albumin, few red blood cells and many white blood cells.

Blood count showed 96 per cent hemoglobin; 5,400,000 red blood cells and 13,900 white blood cells. Blood chemistry was normal.

Phenolsulphonephthalein test revealed the following:

First specimen, 40 minutes after dye injection, 57 c.c. or 13.2%	
Second specimen, 70 minutes after dye injection, 46 c.c. or 14.2%	
Total	27.4%

On April 1, 1935, a right nephrectomy was done by Dr. Farrell. This was followed by a normal postoperative course and with discharge from the hospital on the fifteenth postoperative day.

I again saw this patient on May 17, 1935, at which time I found a two and one-half months' pregnancy. The pregnancy followed a normal course with normal urine and kidney function.

Labor began spontaneously at 6 P.M., Nov. 28, 1935. The patient received 7½ gr. of pentobarbital and 1/150 gr. of scopolamine. At 10 P.M., four hours after the onset of labor, the membranes ruptured and following this one foot prolapsed. She was found to be dilated completely at this time. A left mediolateral episiotomy was done following which the breech and shoulders were delivered with manual aid. Piper forceps were used on the after-coming head. The placenta, which was normal, delivered spontaneously and the episiotomy wound was repaired under gas anesthesia. The baby weighing 5 pounds 6 ounces was perfectly normal.

The puerperium was normal. The blood chemistry, kidney function test, urine and blood pressure were all normal when the patient was discharged from the hospital on her eleventh postpartum day.

The mother and baby were both in excellent condition at the final postpartum examination, six weeks after delivery. The baby was fed entirely with the mother's breast milk.

723 ELM STREET.

## VELAMENTOUS INSERTION OF THE UMBILICAL CORD

A. J. WHITEHOUSE, M.D., LEXINGTON, KY.

(From the Obstetrical Service of St. Joseph Hospital)

THE rarity of a condition imposes the necessity for careful study of every case. Insertio velamentosa is defined as the condition in which "the vessels of the umbilical cord separate at varying distances from the placenta and reach their placental termini by taking their course between the amnion and chorion, or are enveloped in a fold of the former tissue." The incidence is considered about 1 per cent, being higher in multiple than in single pregnancies. Moderate bleeding during the first stage of labor, in the absence of evidence of placenta previa or abruptio placentae, is mentioned as a sign of a condition naturally difficult to diagnose. This follows rupture of its vessels. Only by palpation within the cervix of the pulsating cord vessels over the bulging membranes is absolute diagnosis possible. The condition was not diagnosed antepartum in the case presented.

D. D., twenty-one years old, white, housewife, came under prenatal supervision Nov. 16, 1935. Her last menstrual period began Sept. 6, 1935; menses having been regular and normal previously. Her past history revealed no operations or serious illnesses, except typhoid fever at seven. On May 14, 1935, the patient, on being hospitalized for pyonephrosis with temperature of 104° F., had a spontaneous premature labor at seven months: the baby lived two hours. There were no other pregnancies. The family history was irrelevant.

The present pregnancy was uncomplicated. The patient had a normal increase in weight of about 21 pounds: her blood pressure had ranged from 94 to 110 systolic and 54 to 66 diastolic. There was no edema, no visual disturbance or headache, and no albuminuria. Her medication included 0.5 to 1 gr. of thyroid every day; an iron preparation, Feosol; a fortified cod liver oil; and a course of "Urophosphate," after urine had shown some pus cells at seven months. She felt quickening on Dec. 7, 1935. On May 16, 1936, at 5 A.M., labor began spontaneously and fetal movements were felt. There was no bleeding. The presentation was right occiput anterior. She was given sodium amytal and morphine sulphate early for analgesia. At 11:15 A.M. (about six hours after onset of labor), under light drop ether anesthesia, the patient had an easy spontaneous delivery of a stillborn male fetus weighing 5 pounds 4 ounces. The baby was given an intracardiac injection of adrenalin with no response. It appeared to be a well-developed but marasmic full-term baby. An examination of the placenta and membranes revealed the insertion of the intact umbilical cord in the membranes about 3 cm. from the margin of the placenta. There was no evidence of blood vessel rupture. Autopsy revealed no other demonstrable cause of death.

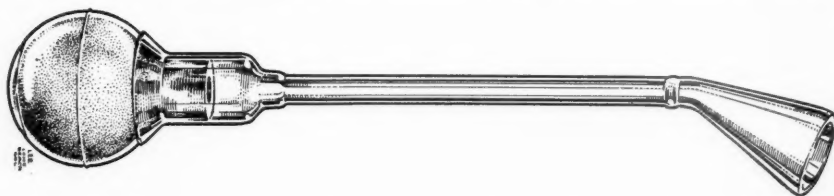
The condition is reported as a possible etiologic factor in stillbirths not otherwise explained.

164 MARKET STREET

## CERVICAL SUCTION SYRINGE

THOMAS L. ROGERS, M.D., LONG BEACH, CALIF.

AS THE cervix has been called the tonsil of the pelvis, the suggestion has been made that a Hurd tonsil suction syringe tube would prove a satisfactory device to remove tenacious mucous plugs from the cervical canal and ducts. This affords a method of obtaining material for smears for diagnosis and also as a cleansing measure preparatory to local applications. Having experimented with the Hurd tube, I found the angle too acute and also felt that if the opening were made circular and larger in diameter, the application would be more effective. At my



request the Becton, Dickinson Company has adapted their regular tonsil suction syringe by lengthening the straight tube and welding on at a 20 degree angle, a funnel-shaped tip with circular opening, either one inch or seven-eighths inch in diameter, inside measurement, as desired. This apparatus has the advantage that the bulb is interchangeable, low priced, and the only deteriorating element. The device can be readily manipulated with one hand and the tip always in sight, it provides adequate suction for the removal of mucopus and establishing drainage. An additional effect is the slight hyperemia produced, which may have a favorable influence on the inflammatory process.

703 PACIFIC AVENUE.

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**Schwartz, I.: Gruskin Intradermal Test for Pregnancy, Am. J. Surg. 33: 225, 1936.**

The simplicity of the test, the rapidity with which diagnosis is made, and the high incidence of accuracy are striking. In the author's series, the test was correctly positive in 96 per cent of 155 pregnant women, and was correctly negative in 90 per cent of 66 nonpregnant women, and all male controls. A group of individuals with disturbed metabolism, usually of endocrine origin or with skin anomalies, are inherently incapable of determinable skin testing. Disregarding this very small group, the test permits of routine application and its validity is asserted by the high percentage of accuracy obtained.

J. THORNWELL WITHERSPOON.

# American Journal of Obstetrics and Gynecology

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EDITORS: GEORGE W. KOSMAK, M.D., AND HUGO EHRENFEST, M.D.

ASSOCIATE EDITORS: HOWARD C. TAYLOR, JR., M.D., AND

WILLIAM J. DIECKMANN, M.D.

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## Editorial Comment

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### Reversal of Sex in the Chick Embryo by the Action of Male and Female Sex Hormones

RECENT experiments by B. H. Willier of the Biological Laboratory of the University of Rochester in collaboration with F. C. Koch and T. F. Gallagher of the University of Chicago (*Physiological Zoology*, January, 1937) have shown that it is possible to alter the sex of chick embryos by injecting known quantities of male and female sex hormones into the developing hen's egg. The female hormones, theelin and theelol (crystalline form, dissolved in ethylene glycol), and the synthetic male hormones, androsterone, dehydroandrosterone, androstenedione (dissolved in propylene glycol), have been used, as well as male hormone preparations from human male urine and bull testis.

Briefly, the method consists of making a single injection of the solutions directly into the albumen through a minute opening in the shell, after forty-eight hours' incubation. Development is continued until just prior to hatching when the embryos are removed from the shell and examined carefully for any changes which may have occurred in their urogenital systems.

With theelin and theelol, dosages ranging from 0.05 mg. to 2 mg., the histologic structure and form of the left testis of the genetic males are markedly modified, consisting of a central core of medullary tissue upon which is superimposed a thick ovarian cortex. The right testis remains testicular in structure but is often smaller than normal. In extreme cases (1 to 2 mg.) no traces of testicular tissue remain in the left testis, reversal is complete, and the gonad is almost indistinguishable from a normal female ovary. In such cases the right testis usually becomes quite flat, reduced in size, and contains ovarian medullary cords. In the genetic females the gonads remain unaffected with the exception of an occasional increase in ovarian cortex on the right.

Oviducts persist in the males and with high dosages become greatly swollen in both sexes. Wolffian ducts (incipient vasa deferentia) remain unmodified.

The asymmetrical differences so noticeable in the response of the two testes are attributed to a germinal epithelium (incipient ovarian cortex) which forms in early development only on the left testis.

With the synthetic male hormones, androsterone, dehydroandrosterone, androstenedione, in doses of from 0.02 mg. to 1 mg., the form and histologic structure of the right ovary of the genetic females are changed to that of a testislike organ. The ovarian medullary tissue is transformed into testis tissue. The left ovary becomes narrower and more rounded than normal and exhibits a thinning of the ovarian cortex and hypertrophy of the ovarian medulla and its inversion to testis tissue. The oviducts of the females undergo a regression beginning distally. Wolffian ducts (potential vasa deferentia) of both sexes are enormously swollen. Within the range of dosages noted above the male gonads remain more or less unaffected. Other workers (Wolf and Ginglinger) using larger dosages (0.5 to 2 mg.) have obtained estrogenic effects in the female, i.e., formation of ovarian cortex on the left testis and persistence of oviducts in male embryos. With male hormone preparations from human male urine, however, in the present experiments definite estrogenic effects were obtained, whether or not the preparation showed the presence of female hormone as detected by the vaginal smear test. In general, recent work with sex hormones in the chick embryo seems to show that it takes more male hormone to bring about reversal of the females than it takes female hormone to bring about reversal of the males.

As regards the manner of action of these hormones, it appears that the male hormones bring about a response of all the potential male components of the bisexual embryonic reproductive system while the female components respond only to the female hormones.



# Department of Practical Problems in Obstetrics and Gynecology

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CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

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## A CONSIDERATION OF THE TYPES AND TREATMENT OF COCCYGODYNIA

EDWARD G. WATERS, M.D., PH.B., F.A.C.S., JERSEY CITY, N. J.

**C**OCCYGODYNIA is a painful neuralgic condition of the tissues in the sacrococcygeoperineal region. It is relatively common in women under forty years of age, is highly disabling and painful, bizarre in its manifestations and types and involves an indeterminate pathology. It is given little attention in literature, texts, or from the profession, and less treatment. Sporadic contributions have discussed the subject matter, but their effects are not lasting. In general, they stress the form of treatment favored by the author, and treat all coccygodynias as a group. The valuable paper of Youngs was "lost" but that of Youmans aroused interest in nonoperative treatment of the condition. The more recent contributions of Lewin and Kleckner, who review the literature, stress the importance of selective therapy, but there still exists a tendency, in most papers, to regard the condition and its treatment as essentially surgical.

### ANATOMIC FACTORS OF IMPORTANCE

Full understanding of the causes, symptoms, effects, and treatment of coccygodynia is dependent upon adequate appreciation of certain anatomic structures. The coccyx is the osseous fusion of the five terminal spinal vertebrae. It is joined to the sacrum above by ligamentous union, and follows its general curvilinear direction. Exceptionally it may be fused or ankylosed. The two coccygeal cornua extend upward from the posterior surface and form, through ligamentous connections with the sacral cornua, important foramina. These transmit the branches of the fifth sacral nerve, the importance of which will be presently seen. The coccyx in the female, in contrast to the male, fuses with the sacrum late in life, if at all. The sacrococcygeal articulation is a false synchondrosis with anterior, superficial and deep posterior, and two lateral ligaments, with a fibrocartilaginous disc interposed. These structures undergo physiologic alterations in late pregnancy which permit increased mobility during parturition. This is especially true of the fibrocartilaginous disc and the anterior ligament. It is highly probable that the relative exposure of the coccyx in female pelvic conformation is an important element in accounting for the greater incidence of coccygodynia in women.

The anterior coccygeal surface has attached to it the levator ani and coccygeus muscles and is in close relationship to the posterior rectal wall.

Laterally attached is the gluteus maximus and at the tip is the attachment of the anal sphincter. The lower strands of the sacrosciatic ligaments are attached near the cornua.

The nerve supply of the region is rich. On the dorsal surface, the posterior divisions of the lower three sacral nerves form loops and, with the coccygeal nerve, supply the skin over the lower end of the coccyx, and send filaments to the posterior coccygeal ligaments. The coccygeal plexiform arrangement of nerves, found along either side, is formed mainly from the anterior divisions of the fifth sacral and the coccygeal nerves. Upon the ventral surface of the coccyx the two symmetrical sympathetic trunks unite and terminate in the single median sympathetic ganglion-coccygeum impar. This ganglion connects with the branches of the fifth sacral and coccygeal nerves, thus forming an extensive plexus on the anterior coccygeal surface. Filaments from this plexiform arrangement pass to the tenomuscular insertions of the levator, coccygeus gluteus maximus muscles, and the sphincter ani. The plexus also innervates the sacrococcygeal joint and ligaments.

Thus it is apparent that the structures which enter into the fusion or support of the sacrococcygeal joint, or influence mobility of the coccyx on the sacrum, are richly supplied by filaments from the coccygeal plexus. Involvement of the sympathetic system through the ganglion impar elucidates to a certain extent the variety of symptoms and the varied causative factors which the condition of coccygodynia may engender.

#### TYPES OF COCCYGDYNIA

It necessarily follows from the above considerations that coccygodynia may be of different types. In this presentation these are arbitrarily grouped as follows:

1. Reflex coccygodynia
2. Traumatic coccygodynia
3. Neuralgia or neuritis of the coccygeal plexus.

*Reflex Coccygodynia—Organic and Psychogenic.*—Reflex coccygodynia is symptomatic of systemic disturbance removed from the local site. It is of two types, organic and psychogenic. Some of the conditions which may be listed under organic reflex coccygodynia are rectal tabes, meningiomas, spinal fractures, spina bifida occulta, and postmeningitic states. Personally, we have seen none of these, although they are mentioned by Simpson, Drueck, Kleckner and others. Many patients are seen with rectal troubles, especially fistulas, piles, proctitis, and fissures, where there is referred perianal pain erroneously referred to the coccyx. Only a careless examination could fail to reveal the true type and cause of pain. They do not cause coccygodynia, but coexistence with true coccygodynia may produce embarrassing confusion.

Psychogenic coccygodynia is attributed to hysteria, neurasthenia, psychoneurosis, traumatic neurosis, and patients with "irritable spine"; somewhat frequently seen as a causative factor is definite sex imbalance or maladjustment. Hamill recites an interesting case based upon hysteria and expresses the opinion that the spasmodic pains of coccygodynia are analogous to vaginismus, and that all cases should be handled by psychotherapy. Except for reflex coccygodynia of psychogenic origin, which is by no means common, this view is at variance with most clinical opinion and experience.

*Traumatic Coccygodynia.*—Coccygodynia of traumatic origin is the oldest of recognized types. There may be an obvious and palpable dislocation or fracture of the coccyx as a result of a blow, kick, or fall. Infection after operation for pilonidal cyst may result in chronic pericoccygitis, and acute sacrococcygeal arthritis has been seen following trauma, exposure, and acute upper respiratory infections. An ankylosed coccyx may be broken during delivery, especially if a narrow pubic arch forces the fetal head to ride through the posterior triangle of the outlet. But we have known this to occur many times with coccygodynia an infrequent sequel, whereas the latter has been frequently seen after falls and external violence. In our experience, if a palpable deformity exists in association with coccygodynia, it is a forward dislocation of the coccyx, almost never a posterior luxation. Horseback riding is usually mentioned with the etiologic factors. The only such case in our experience occurred in using a mechanical gymnasium horse.

*Neuralgia and Neuritis of the Coccygeal Plexus.*—The third and largest group of the coccygodynias is that comprising neuralgia and neuritis of the coccygeal plexus. This formed over 60 per cent of the fifty-three patients studied for this condition. Such patients are those without history or findings of gross or discoverable injury to the coccyx, and who have neither organic nor psychogenic factors operating which would label the pain as reflex.

Neuralgia exists when there has been transient injury of the overlying coccygeal tissues, as in parturition, with subsequent inflammatory reaction, edema, and secondary fibrosis resulting in pinching, pressure or chronic irritation of the highly susceptible plexus. If the local condition is severe or suppuration occurs or the damage to the nerves is great, an actual neuritis supervenes, with the chance of spontaneous cure less.

Clinically, neuralgia and neuritis of the coccygeal plexus are sharply differentiated from the traumatic group. In the reflex type, the history and examination show an anorectal or systemic affection without tenderness or pain definitely localized in the coccygeal region. In the traumatic type, there is usually obvious or palpable deformity with aggravation of the pain on coccygeal motion. However in the neuralgic or neuritic type, while passive motion of the coccyx may be entirely painless, contraction of the levator ani muscle, stool evacuation, pinching the tissues at the tip of the coccyx, pressure on the ventral coccygeal surface or over the sacrococcygeal joint, may induce exquisite pain, reproducing that for which the patient seeks relief. The pain is well localized to the anococcygeal body. When there is pain radiation into the back, buttocks, or legs, some other causative condition must be sought for. It is only in reflex coccygodynia that there is notable pain radiation.

It is highly important not to adjudge a patient with true coccygodynia of the traumatic or neuralgic types a psychoneurotic because of nervous manifestations developing in the course of the illness. The marked disability from continuous or recurrent pain is conducive to changes suggesting nervous imbalance, especially in those with low pain tolerance. Psychiatric therapy can hardly be effective when the primary factor continues to operate, although one cannot minimize the value of associated suggestive therapy.

## TREATMENT

The partition of coccygodynia according to causal type simplifies the problem of therapy. In reflex coccygodynia, no benefit may be expected from purely local therapy. A careful history and examination of the entire patient with detailed observation of the exact type, location and radiation of pain should reveal the cause for reflex coccygodynia. The proper and only effective treatment is to deal with the causative condition. It is well to remember that more than half of the reflex coccygodynias are caused by sexual imbalance or maladjustment. The physician interested in these peculiarly human problems can completely relieve the sufferer by combining psychotherapy with alleviation or correction of the sexual disaffection.

Treatment of traumatic coccygodynia is definite. In the acute stage, bed rest is indicated with local applications of heat in the form of hot sitz baths, hot oil rectal instillations, hot rectal douches, diathermy or short wave therapy. A dislocated coccyx is manually reduced, if possible. Analgesics and sedatives are certainly indicated, with dosage sufficient to give clinical relief. The acute phase is over in ten to twenty days, and the patient often obtains complete relief in spite of a persisting coccygeal deformity. When the pain becomes chronic, resort may be had to two lines of action, radical or conservative. The radical procedure of coccygeal excision, although surgically simple, should be deferred until conservative therapy has received a thorough trial. The coccyx serves as an important point of musculotendinous attachment, and its removal leaves some degree of pelvic weakness. The operation may be complicated by a disabling infection, and not infrequently after the coccyx is out, the pain still persists. Therefore the operation is neither to be suggested nor lightly undertaken until conservative measures fail, or unless there is gross deformity, caries, osteomyelitis or coccygeal periostitis with pericoccygitis.

Neuralgia and neuritis of the coccygeal plexus are best treated by direct attack on the plexus. Injections of novocaine, alcohol, benacol, quinine and urea hydrochloride, sodium morrhuate, and saline were used in this series. While all were found of some value, the most useful solutions were 2 per cent novocaine in 2 c.c. to 10 c.c. amounts, and  $\frac{1}{2}$  to  $1\frac{1}{2}$  c.c. of 80 per cent alcohol. From one to six injections of novocaine are required, and the relief obtained is usually permanent. Injection of alcohol, suggested by Youngs and Youmans, follows DeVesian's application in 1907 of trifacial nerve injections based upon Schlosser's principles. These are more definite and lasting in effect, but they are also more painful; two of our patients had prolonged pain with induration, redness, and swelling which lasted for ten days, following a 3 c.c. injection of 80 per cent alcohol. Rather marked induration and inflammatory edema may be expected in the perineal body and pericoccygeal tissues should more than  $1\frac{1}{2}$  c.c. of 80 per cent alcohol be injected. This tender area gives rise to an aching sensation in the rectal region for a week or more, but it is generally tolerated better than the coccygeal pain which it supplants. Some degree of asymptomatic tissue induration is commonly seen even with small doses.

The following is a description of the technic employed in our cases. The patient is placed in the right lateral Sims position for all injections, excepting those made on the anterior surface or concavity of the coccyx, when the exaggerated lithotomy position is used. The gloved index

finger of the left hand is introduced into the rectum and the region is carefully palpated between it and the thumb externally. The shape and structure of the coccyx are determined and the position of the spot of greatest tenderness is carefully noted. This is usually at the tip of the coccyx, 1 cm. beyond the tip in the perineal body, or at the sacro-coccygeal joint. At first the entire area may be noted as tender, but a persistent search will locate one spot of exquisite tenderness. This marks the site of the first injection. The skin is sterilized with 3½ per cent iodine on a cotton applicator, and the injection made with the right hand, the fingers of the left hand remaining in situ to definitely locate and place the injection, as well as guard against rectal perforation. Three to 6 c.c. of 2 per cent novocaine solution are used for the initial injection, and repeated every five to seven days until complete relief is obtained. Four injections usually suffice. If the coccygodynia is sharply localized to a spot in the perineal body, ½ c.c. of 2 per cent novocaine is injected, followed in a moment, without withdrawing the needle, by 1 or 1.5 c.c. of 80 per cent alcohol. Where the pain is localized on the ventral surface of the coccyx, the extreme lithotomy position will permit insertion of a long needle through the perineal body past the tip of the coccyx and into the coccygeal plexus. The injection may also be made through an approach on either side of the coccyx. One may elect to seal the injection site with collodion, but this is not necessary. The patient is instructed to take mineral oil or petroleum-agar emulsions, continue a usual diet, and employ sitz baths or hot oil enemas to relieve the aching pain or soreness occasionally experienced.

No serious complications will result if the above instructions as to type, amount, and placement of injections are followed. The two very severe reactions in 53 patients were due to injection overdosage of alcohol.

The results are excellent. In this series, 41 were clinically cured. Ten did not complete the series and of these, 6 later reported marked improvement. Four were not traced. Two patients received severe reactions, refused further treatment, and are recorded as having been adversely affected by treatment.

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# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Endocrinology

**Balashova and Sicheva:** Capillaroscopy in Some Endocrine Diseases, *Vestnik Endocrinol. (Moscow)* 5: 632, 1935.

The authors investigated by means of a capillaroscope the capillaries of the nail beds, the skin of the back of the wrist and the foot, and in some patients the skin of the forearm in cases of diseases of endocrine glands. In 40 cases of hypofunction of the ovaries atony of the capillaries was found and in the capillary loop the venous branch was dilated. The blood stream was slower and in the majority of loops there was stasis. The stream is not always homogenous, often there was a granular appearance. The subpapillary net was dilated. Clinically wrists were cyanotic, edematous, and moist. Fingers were large with short, thick and dim nails and very pale. Cutis marmorata was noted especially on the extremities.

In hypoplasia and aplasia of the sexual apparatus (early eunuchoidism), there was noted delay in the development of the ectodermal capillary net.

In cases of amenorrhea on the basis of general infantilism there was found a hypoplastic net of capillaries with a multitude of aneurysms.

There was a close similarity in the picture of the capillaries in the cases of obesity of hypophyseal-ovarian type, dystrophia adiposo-genitalis and obesity due to ovarian insufficiency. The outstanding characteristic for the majority of cases was unusually fantastic and a great variety of forms of capillaries due to their extreme tortuosity and large amount of aneurysm, long loops curled up; the blood stream was often slower than normal.

ALEXANDER GABRIELIANZ.

Werner, A. A.: Syndrome Accompanying Deficiency or Absence of the Ovarian Follicular Hormone, *Endocrinology* 19: 695, 1935.

This article is based upon an analysis of the objective signs and subjective symptoms presented by 197 women having deficiency or absence of the ovarian follicular hormone. This group of patients consists of 53 castrates, 96 women in the menopause and 48 subjects having involutional melancholia. The subjective symptoms are classified as nervous, circulatory and general. That these symptoms do accompany ovarian hypofunction or afuction is evidenced by their regularity of occurrence in 53 castrates studied. This same train of symptoms is found with striking parallelism in the menopause and involutional melancholia.

J. THORNWELL WITHERSPOON.

**Goecke, Herman:** The Action of the Male Sex Hormone (Testicular) at the End of Pregnancy, *Ztschr. f. Geburtsh. u. Gynäk.* 112: 273, 1936.

The author was able to demonstrate the presence of the male sex hormone in 71 per cent of the placentas of female fetuses examined. He was never able to detect

the hormone in the placentas of male fetuses. In the case of twins of opposite sex, the placenta of the female only contained the male sex hormone. He believes that the male hormone is utilized by the male fetus in intrauterine life, and therefore is absent in the placenta. In the cases of hydatiform mole no male hormone was demonstrable in the cystic masses found in the uterus. The urine of these patients contained large amounts of the hormone. From this fact the author concludes that there is no definite relationship between the amount of hormone found in the placenta and the amount excreted in the urine. He also found that the male sex hormone was present in the urine at the end of pregnancy only when a male child was to be born and never when the child was to be a female. This is explained as follows: Although the placenta of a male fetus produces large amounts of the m.s.h., it quickly passes into the blood stream, because of the great requirements of the fetus, and is excreted in the urine. The female fetus does not require the hormone for its own use, so that it remains stored up in the placenta, and is not found in the blood stream or in the urine. The author believes that the sex of the unborn child can be determined in at least 80 per cent of the cases, for in that number a minimum of one cock unit of hormone is present in three liters of urine in the case of a male child, whereas none, or at least less than one cock comb growing unit, is present in a similar amount of urine in the case of a female child.

E. S. AUER.

**Deanesly and Parkes: Oestrogenic Action of Compounds of the Androsterone-Testosterone Series, Brit. M. J. 1: 257, 1936.**

Extracts of testis and male urine contain estrogenic substances of the estrone group. It is now recognized that substances similar in chemical nature to estrone may have some degree of estrogenic power. It has been possible to hydrogenate estrone, which itself shows no male hormone activity, to a substance having male hormone activity but no estrogenic power. The first male hormone obtained, androsterone, isolated from male urine was nonestrogenic by the vaginal cornification test and by a plumage test. Recently Butenandt and Kudzusz reported that trans-dehydroandrosterone, androstenedione, and testosterone cause opening of the vagina in the intact immature rat. Trans-dehydroandrosterone is present in male urine. Androstanediol increases the size of the uterus and vagina of the adult ovariectomized rat. It seems likely that the estrogenic action of testis and male urine extracts may be due to the presence of compounds exerting an estrogenic action, rather than the actual presence of estrone or some other purely estrogenic compound.

F. L. ADAIR AND S. A. PEARL.

**Seguy, J.: Virilism Among Puberal Women, Gynéc. et obstét. 33: 215, 1936.**

Virilism in women is characterized by two groups of symptoms. First there is regression of secondary feminine sexual characteristics such as the disappearance of menstruation, atrophy of the breasts, and loss of fat in various parts of the body. On the other hand, secondary masculine sex characteristics appear. For example the clitoris enlarges, the voice becomes masculine and the general body contour changes. Virilism, therefore, consists essentially of changes in the secondary sex characteristics without involvement of the primary sex organs. It is due to a disturbance in one or more glands of internal secretion. The chief type of ovarian disturbance which is responsible for virilism is arrhenoblastoma of the ovary. Virilism may also be caused by corticosuprarenal lesions, anterior hypophyseal disturbances and thyroid diseases. The treatment of virilism varies considerably. If a unilateral ovarian tumor is found it should be removed, likewise a tumor of the suprarenal gland. If x-ray pictures demonstrate a tumor of the hypophysis this

tumor should be enucleated. If no tumor is discovered in the pelvic region, lumbar region, or hypophyseal area, the treatment is much more difficult. The author suggests various forms of hormone therapy, depending upon the endocrine organ or organs suspected as being responsible for the virilism.

J. P. GREENHILL.

**Ahumada and Calatroni:** Arrhenoblastoma of the Ovary, *Bol. Soc. de obst. y ginec.* (Buenos Aires) 15: 488, 1936.

The patient prior to removal of the ovarian tumor had marked masculine distribution of hair, with a male figure, and marked elongation of the clitoris. Soon after removal of the arrhenoblastoma the masculine characteristics began to diminish and now, after a period of four years, female characteristics predominate.

MARIO A. CASTALLO.

**Falkiner, Ninian McL:** Relation of the Ovarian Cycle to Endocrinology, *Brit. M. J.* 1: 149, 1936.

The author presented eight specimens of human corpora lutea removed at different stages in the menstrual cycle and attempted to correlate the significance of hemorrhage into the corpus luteum. This hemorrhage, the author claims, is synchronous with the bleeding from the uterine mucosa of menstruation. In the corpus luteum of pregnancy no such gross hemorrhage could be demonstrated.

"The administration of luteal extracts in the present state of our knowledge is not of great clinical use." The author believes, however, that the administration of progestin in cases of threatened and repeated abortion may be useful. The corpus luteum extract may produce a satisfactory condition for embedding the ovum, and it may help to maintain the early decidua in a condition suitable for the development of the placenta. It may also aid in reducing the liability of abortion by reducing the irritability of the uterine muscle, making it less likely to undergo contractions. Further studies in this field are essential.

F. L. ADAIR AND S. A. PEARL.

**Ehrhardt, K., and Fischer-Wasels, H.:** Study of the Content of Corpus Luteum Hormone in the Human Placenta, *Monatsschr. f. Geburtsh. u. Gynäk.* 102: 80, 1936.

The authors found that the amount of corpus luteum hormone in the mature human placenta is inconstant and small, having been found only in 8 per cent of the cases studied. However, this hormone was present more frequently in immature placentas of women between the sixth and eighth months of pregnancy. No hormone could be found in placentas of pregnancies less than four months old. Extracts of placentas from patients with eclampsia and preeclampsia gave positive results for the hormone but no conclusions should be drawn from this concerning the etiology of the toxemias of pregnancy.

The parenteral administration of corpus luteum hormone failed to lead to the detection of the hormone in the urine. Hence this hormone like the follicle hormone is inactivated in the body. The corpus luteum extract had a marked stimulating effect on the breasts of infantile rabbits.

The studies of the authors are of practical significance because they show which placentas are useful for their corpus luteum hormone effect. The most valuable placentas are those obtained at the sixth, seventh, and eighth months of gestation, after which came those of the fifth and ninth months. In two cases of habitual

abortion the authors succeeded in maintaining the pregnancies to term by giving extracts of placentas obtained from the sixth and seventh months. In cases of uterine hypoplasia, a definite growth of the uterus could be obtained with placental extracts.

J. P. GREENHILL.

**Guldberg, E.: Sites of Production of the Sex Hormones in Normal Pregnant Women in the Light of Hormone Analysis After Oophorectomy During Pregnancy, Acta obst. et gynec. Scandinav. 15: 343, 1936.**

A critical survey of the literature indicates the correctness of Halban's theory, first promulgated in 1905, that the placenta is the seat of hormone production during pregnancy. Particular emphasis must be placed on the increasing number of reports of cases in which bilateral oophorectomy is performed early in pregnancy without interrupting the gestation. This indicates the wholly subordinate rôle played by the ovary. The fetus likewise is not important for maintenance of the pregnancy as evidenced by the continued development of gestations in the presence of hydatid moles.

Hormone studies during pregnancy in women whose ovaries were removed have proved that folliculin, the corpus luteum hormone and the gonadotropic hormones are produced in the placenta. There is a biologic difference between the follicle maturing hormone secreted during pregnancy and in the castrated state.

J. P. GREENHILL.

**Bandler, U: Gonadotropic Hormones in the Urine of Women With Tumors, Monatschr. f. Geburtsh. u. Gynäk. 102: 156, 1936.**

In a series of 21 women who had squamous cell carcinoma of the cervix, Bandler found gonadotropic hormones in the urine in 72.7 per cent before treatment was instituted. The amounts of hormone varied between 80 and 500 mouse units per liter of morning urine. After the first x-ray treatment there was a decrease in the amount of hormone in the urine. The level rose before the second treatment and then again decreased. In untreated cases of adenocarcinoma of the cervix, these hormones could be found in only half of the cases. The hormones were found in 78 per cent of untreated women with squamous cell carcinoma of the vulva. They could not be detected or only in very small amounts in women who had benign tumors and gynecologic illnesses.

J. P. GREENHILL.

**Vincent, B., and Lewis, Robert M.: The Induction of an Acid Vaginal Secretion in the Immature Macaque by Injection of Estrin, Endocrinology 20: 210, 1936.**

In 6 immature macaques pH determinations proved the vaginal fluid to be definitely alkaline. Three monkeys were then injected over a period of two weeks with sufficient estrin to cause reddening of the sexual skin and to produce hyperplasia of the vaginal mucosa.

The vaginal fluid of the injected animals was found to be highly acid. An increase in the H-ion concentration of at least 2 pH units was observed in each case. After withdrawal of the hormone and the subsequent return of the vaginal mucosa to the condition normal for the immature animal, the vaginal fluid was found to return to its former alkalinity.

In one animal the vaginal fluid showed pH 7.8 forty-eight hours before reddening of the sexual skin occurred. With the discoloration an extraordinarily rapid shift

took place giving a H-ion concentration of 5. A similar but less abrupt change of flora and vaginal acidity associated with normal puberty in girls has been described by Socken.

The results of similar observations on children, briefly detailed, indicate that this response to the injection of estrin may explain the favorable results which have been reported in the treatment of infantile gonorrheal vaginitis.

J. THORNWELL WITHERSPOON.

**Hisaw, Frederick L., and Lendrum, Frederick C.: Squamous Metaplasia in the Cervical Glands of the Monkey Following Estrin Administration, Endocrinology 20: 228, 1936.**

The authors have confirmed the observations of Overholser and Allen, and of Engle and Smith, that prolonged estrin stimulation produces in the cervix of the monkey a condition of squamous cell metaplasia which resembles beginning malignancy in the human female. Stimulation of the monkey's own ovaries to produce estrin by administration of anterior pituitary preparations is usually not followed by squamous metaplasia. Simultaneous corporin therapy will inhibit the action of estrin in evoking squamous metaplasia in the cervix. The cervical lesions apparently undergo regression, either spontaneously when all treatment is withdrawn, or under the influence of corporin even when estrin is continued.

J. THORNWELL WITHERSPOON.

**Dallera, Nicolo: Modification of Uterine Epithelium Under Hormonal Influences, Folia gynaec.-demogr. (Genova) 33: 8, 1936.**

The author describes the histologic modifications of the uterine mucosa of rats, during the stage of prolan A blood saturation and during the injections into these animals of folliculin. He discusses on the basis of the alterations observed, experimental hormonal conditions which give rise to the marked epithelial transformations observed, and those which occur normally in women during those years when carcinoma of the uterus is more prevalent.

The author makes a plea for further studies along this line, in order that the cause of carcinoma may be better approached.

MARIO A. CASTALLO.

**Damm, P. N.: Examination of the Changes in the Uterine Mucosa Following Excessive Doses of Follicular Hormone, Acta obst. et. gynec. Scandinav. 15: 58, 1935.**

In a twenty-nine-year-old castrated woman treated with 750,000 M. U. of follicular hormone, Damm observed changes in the atrophied endometrium which correspond to glandular-cystic hyperplasia. From this experience the author warns that large doses of follicular hormone should not be used on patients with deficient or inactive ovaries unless followed up by treatment with progestin.

J. P. GREENHILL.

**Witherspoon, J. Thornwell: Hormonal Origin of Endometrioma, Arch. Path. 20: 22, 1935.**

Witherspoon advances the hypothesis that the igniting factor which stimulates the endometrial implant to proliferation is the ovarian follicular hormone. The morphologic and functional characteristics of an endometrioma and of the uterine endometrium are similar; the integrity and function of the endometrioma are



dependent on the presence of active ovarian tissue; the endometrioma gives a decidual reaction during pregnancy and undergoes the phases of the menstrual cycle. It therefore appears highly probable that the estrogenic principle is essential for the maintenance of the lesion. In 64 per cent of 44 cases studied it was found that ovarian and uterine endometriomas were associated with endometrial hyperplasia, a figure too high to indicate a mere coincidence. Not only are the uterine and the aberrant endometrium stimulated to hyperplasia and tumor proliferation, but the uterine musculature also is affected. Functional uterine hemorrhage and sterility that are associated with endometrioma may also be explained and accounted for according to this hypothesis. The frequency of sterility (60 per cent) with endometrioma is due to the presence of multiple follicular cysts of the ovaries in the absence of ovulation and of the formation of corpora lutea.

W. B. SERBIN.

**Tapfer and Haslhofer: Enlargement of the Pelvis by Means of Hormones in Animal Experiments, Arch. f. Gynäk. 159: 313, 1935.**

The authors discuss the considerable expansion of the pelvis which takes place in pregnancy from a relaxation of the symphyseal and sacroiliac joints as the result of hormonal stimulation. All investigators agree that such expansion is due to hormonal influences, but nobody has as yet determined exactly which hormone is responsible for such joint changes.

The authors used the blood serum of pregnant rabbits in nonpregnant guinea pigs and observed dilatation and relaxation of the pubic joints which grossly and microscopically were exactly the same as those produced by pregnancy. The nearer term the rabbit was, from which the serum was taken, the greater was the joint reaction. The intensity of the reaction does not, therefore, follow the degree of corpus luteum hormone concentration but rather that of estrin. Apparently the estrogenic hormone produces these characteristic joint changes. The authors also experimented with commercially prepared hormones and again found that the estrogenic hormone caused these characteristic changes.

RALPH A. REIS.

**MacDonald, Ian G.: The Response of the Mammary Gland to Prolonged Stimulation With Ovarian Hormones, Surg. Gynec. Obst. 63: 138, 1936.**

The continuous administration of the ovarian hormone estrin in castrated rabbits produces, at first, a generalized overgrowth and ramification of the ductal system in the mammary gland with practically no acinar growth.

Carried further (100 days), little gross change occurs, but atypical histological variations appear in the ductal epithelium which often verge on the borderline of neoplastic changes.

When such stimulation is prolonged for six months or more, both the gross ductal growth and microscopic epithelial hyperplasia regress to a nearly resting state. Ductal widening is not prominent under pure estrin stimulation.

In rabbits the response of the ductal system of the breast and its epithelium to continuous estrin stimulation is confined to certain limits, past which a refractory state is set up.

Estrin and corpus luteum extract in combination produce both ductal and acinar overgrowth; early secretion occurs and the ducts become distended.

Dilation of the ducts is probably mechanical from distention by secretion, and not a specific effect of estrin.

Estrin and progestin, on the basis of present evidence, do not produce specific pathologic lesions, cystic disease and adenosis.

WM. C. HENSKE.

**Mortimer, Wright, and Collip: The Effect of Oestrogenic Hormones on the Nasal Mucosa; Their Rôle in the Naso-Sexual Relationship; and Their Significance in Clinical Rhinology, Canad. M. A. J. 35: 615, 1936.**

A review of the literature on the behavior of the conchal mucosa in relation to the sex cycle is given. A comparison of the nasal cavities of the human and monkey is made and individual variations are indicated. A careful control in the series of 28 monkeys, which were studied, is described. A rhinologist examined the nasal cavity weekly without individual identification or knowledge of the menstrual cycle. The menstrual cycle of monkeys was recorded by others. It was ascertained that the estrogenic hormones exert definite influence upon the conchal membrane. Crystalline estrone and estriol and emmenin produce redness and swelling similar to the changes in other sex-skin areas. This is obtained also in castrated animals and in males.

Studies next were begun in women. It is apparent that the hormones of the ovary exercise a specific physiologic influence upon the mucous membrane of the conchae. Thus it is evident why the rhinologist should bear in mind the possible alteration of the mucosa from factors other than primary rhinitis, such as pregnancy and various stages of the menstrual cycle. Finally, estrogenic hormone substances may be employed in certain cases of atrophic rhinitis and are thus of particular interest to the rhinologist.

H. CLOSE HESSELTINE.

**Friedgood, H. B., and Pincus, G.: Nervous Control of the Hypophysis, Endocrinology 19: 710, 1935.**

Thirty-two adult female rabbits were isolated in separate cages for a period of three to four weeks before being used in the present investigation. Faradic stimulation of the cervical sympathetic nerves was carried out in 6 of these animals, while 3 of them (controls) were subjected to the same operative procedures up to but not including the stimulation of their cervical sympathetics. The remaining 23 rabbits (also controls) were sacrificed after their period of isolation. None of the controls showed either ovulation or microscopic evidence of ovum maturation; whereas each of the 6 rabbits which had their cervical sympathetics stimulated revealed extensive maturation of their ova, and ovulation occurred in 3 of them. It is concluded from these results that the rate of secretion of the gonadotropic principle can be experimentally increased by faradic stimulation of the sympathetic fibers which innervate the anterior hypophysis. These experiments also indicate that the cervical sympathetic nerves may be at least partially responsible during coitus for stimulating the anterior hypophysis to release its gonadotropic secretions in increased amounts.

J. THORNWELL WITHERSPOON.

**Zondek, Bernhard: The Inhibitory Effect of Follicular Hormone on the Anterior Lobe of the Pituitary Gland, Lancet 1: 10, 1936.**

This report indicates that the follicular hormone inhibits the hormonal function of the anterior pituitary. Infantile rats were used and controls carefully made. The preparation was given subcutaneously twice a week as a-hormone in aqueous or oily solution, or the benzoic ester of dihydrofollicular hormone (Dimenformon). The control animals received injections of normal saline or olive oil. When 100 M.U. were given no effects on body growth resulted, but when 1,000 M.U. twice a week were given definite inhibition of growth occurred.

The prolonged application of the hormone induces a continuous estrus. The vagina and uterus enlarge and the lining membranes proliferate. Abundant corpora lutea are found in the control animals but they are absent in the treated

ones. The ovaries are retarded in their development. The male genital organs are completely arrested in their development by folliculin. The larger the amount of hormone the greater the inhibition of growth. "Follicular hormone paralyzes the gonadotropic hormones of the anterior pituitary—and seemingly the luteinizing hormone, prolan B, in particular—thus hindering them from exerting their normal influences on the ovaries."

H. CLOSE HESSELTINE.

**Zondek, Bernhard: Impairment of Anterior Pituitary Functions by Follicular Hormone, Lancet 2: 842, 1936.**

The ovarian function depends upon the gonadotropic hormones of the anterior lobe of the pituitary. Small doses of estrin stimulate the function of the anterior lobe while large ones depress it. In the animal (rat and chicken) small amounts produce proliferation of the uterine mucosa, but large amounts cause cystic hyperplasia and ultimately destruction, necrosis and aseptic suppuration.

Because the growth hormone balance is affected later, the cells producing gonadotropic hormone are the more sensitive. The growth is altered by action upon the bone growth. The follicular hormone does not inhibit the mechanism of production but only the mechanism of secretion. Hence the anterior pituitary functions are not equally and simultaneously affected. Growth is not resumed after several months of estrin treatment unless Evans's pituitary growth hormone is administered, which proves that the dwarfing was of pituitary origin. Moreover, the follicular hormone does not inhibit the production of the gonadotropic hormones in the anterior lobe cells but only prevents them from entering the blood stream.

The experimental animal differs significantly from the hypophysectomized one.

H. CLOSE HESSELTINE.

**Jones, M. S., and MacGregor, T. N.: Inhibitory Effect of Follicular Hormone on the Anterior Pituitary in Humans, Lancet 2: 974, 1936.**

The authors attempted to inhibit the gonadotropic and the diabetogenic principle of the anterior pituitary by giving large doses of estrin. The ten experimental subjects were all chronic psychotic patients between the ages of fifty-two and eighty-three (average 62.6). Metabolic and endocrine fluctuations due to emotional causes were improbable. The amount of gonadotropic hormone in the urine and a sugar tolerance curve were established before administering 500,000 to 1,000,000 M.U. estrin (Dimenformon) in a period of twenty days. Seven of the ten women had bleeding from the uterus. The psychopathic state remained unaltered.

This procedure caused the excretion of the gonadotropic hormone, which had exceeded 50 M.U. per liter, to be abolished. No consistent effect on the glucose tolerance test resulted.

H. CLOSE HESSELTINE.

**Zondek, Bernhard: Tumour of the Pituitary Induced With Follicular Hormone, Lancet 1: 776, 1936.**

Under administration of follicular hormone to animals the gonads underwent complete atrophy while the pituitary enlarged in all cases of males, but macroscopically remained unaltered in the females. The functional inhibition of the anterior lobe of the pituitary appeared equally in males and females. The growth of the pituitary is not responsible for this change.

The author produced dwarfed animals with hypoplastic genitals by prolonged administration of follicular hormone.

H. CLOSE HESSELTINE.

**Karlik, L. N.:** *Rare Case of Pregnancy and Delivery in an Hypophysectomized Bitch*, *Vopr. Endocrinol.* (Moscow) p. 809, 1936.

Contrary to the belief of all experimental workers that pregnancy cannot take place in the hypophysectomized animal, the author reports a case of a grown bitch of 7 kg. on which hypophysectomy was performed on Oct. 19, 1932 through the temporal route. The dog increased in weight shortly to 8.5 kg. On March 15, 1933, the right lobe of the thyroid gland and the right parathyroid glands were removed. Later on the bitch was kept with other hypophysectomized dogs of both sexes for five or six hours daily. Feb. 3, 1934, 478 days after hypophysectomy, the bitch gave birth to one puppy. The puppy suckled vigorously, but died the next day. On autopsy every organ, including the skeletal and muscular systems, were found normal. The stomach was absolutely empty. In the mother's mammary glands, no traces of milk were found. April 13, 1934, the bitch died in an experiment with the injection of insulin. The autopsy confirmed the absence of the hypophysis.

ALEXANDER GABRIELIANZ.

**Fagioli, Mario:** *X-Ray Study of the Cranium in Women With Ovarian Dysfunction*, *Ginecologia* (Torino) 6: 625, 1935.

On the basis of radiographic studies on twenty-four women the author affirms that in the presence of secondary ovarian insufficiency the sella turcica appears in variable forms and usually is larger. In these cases also calcification of the pineal body is frequently noticed.

AUGUST F. DARO.

**Thaddea, Sigismund:** *Relationship Between Adrenal Cortex and the Gonads*, *Ztschr. f. Geburtsh. u. Gynäk.* 110: 225, 1935.

The author believes that the hormones of the adrenal cortex influence gonadal function by way of the anterior lobe of the pituitary, as well as regulate the metabolism of carbohydrates. He also demonstrates a close relationship between the hormones of the adrenal cortex and vitamin C. During pregnancy there is an increased demand for the hormone of the adrenal cortex. In cases of pregnancy associated with Addison's disease there is an increased sensitivity to toxins. Hyperemesis and adynamia are markedly increased in severity. In these cases sodium chloride therapy is indicated because both conditions cause a loss of blood chlorides. In severe cases of Addison's disease complicated by pregnancy, the latter must be terminated because administration of adrenal cortex extract does not stop the progression of symptoms. Mild cases may be carried to term with proper treatment with adrenal cortex hormones.

EUGENE S. AUER.

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## Books Received

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ERGEBNISSE DER MEDIZINISCHEN STRAHLENFORSCHUNG. Herausgegeben von Holfelder, Holthusen, Juengling, Martius und Schinz. Band VII. 622 Seiten mit 294 Abbildungen im Text. Verlag von Georg Thieme, Leipzig, 1936.

FILLE OU GARÇON. Par Docteur Jules Regnault. Editions Medicis, Paris, 1936.

THE EGGS OF MAMMALS. By Gregory Pincus, Assistant Professor of General Physiology, Harvard University. 160 pages, illustrated. The Macmillan Company, New York, 1936.

**PROSTITUTION.** By Tage Kemp, M.D., Copenhagen. Translated from the Danish by Elsie-Marie Werner Kornerup. 253 pages. Levin & Munksgaard, Copenhagen, 1936.

**GYNECOLOGY AND OBSTETRICS.** By Edwin M. Jameson, M.D. Surgeon, General Hospital, etc., Saranac Lake, N. Y. 170 pages with 5 illustrations. Paul B. Hoeber, Inc., New York, 1936.

**DIE BEKAEMPFGUNG DER EKLAMPTISCHEN SCHWANGERSCHAFTS-ERKRANKUNGEN.** Von Heinrich Siedentopf, Oberarzt der Universitaets-Frauenklinik zu Leipzig. 86 Seiten. Johann Ambrosius Barth, Leipzig, 1936.

**THERAPEUTICA DAS SYNDROMES GRAVIDO-PUERPERAES.** Par Dr. Joao Pereira de Camargo, livre docente de medicina da Universidade do Rio de Janeiro, etc. 2. a edição correcta e muito augmentada. 376 pages. Freitas Bastos, Rio de Janeiro, 1936.

**FACTS AND FRAUDS IN WOMAN'S HYGIENE.** By Rachel Lynn Palmer and Sarah K. Greenberg, M.D. 311 pages. The Vanguard Press, New York, 1936.

**PHYSICIAN, PASTOR AND PATIENT.** Problems in Pastoral Medicine. By George W. Jacoby, M.D. 390 pages, illustrated. Paul B. Hoeber, Inc., New York, 1936.

**MEDICINE AND MANKIND.** Lectures to the Laity delivered at the Academy of Medicine in New York. Edited by Jago Galdston, M.D. 217 pages. D. Appleton-Century Company, New York, 1936.

**MEDICAL MORALS AND MANNERS.** By Hubert Ashley Royster, M.D. 333 pages. Chapel Hill, The University of North Carolina Press, 1937.

**DISEASES OF THE NEWBORN.** By Abraham Tow, M.D. Adjunct Professor of Pediatrics, New York Polyclinic Hospital, etc. Illustrated, 477 pages, Oxford University Press, New York, 1937.

**INTO THE UNIVERSE.** The Story of Human Birth. By Alan Frank Guttmacher, Associate in Obstetrics, Johns Hopkins University. Illustrated, 366 pages. The Viking Press, New York, 1937.

**UEBER DIE GEBURTSTRAUMATISCHEN SCHAEDIGUNGEN DES ZENTRALNERVENSYSTEMS.** Von Dr. Med. H. Nevinny, Universitaets-Frauenklinik in Koenigsberg, Pr. Mit 8 Textabbildungen und 12 Tafeln, 87 Seiten. Ferdinand Enke, Stuttgart, 1936.

**PÉRIODES DE FÉCONDITÉ ET DE STÉRILITÉ CHEZ LA FEMME.** Par H. Vignes et M. Robey. 85 pages. Masson et Cie., Paris, 1936.

**INHALATION ANESTHESIA.** By Arthur E. Guedel, M.D. Associate Clinical Professor of Surgery (Anesthesia), University of Southern California School of Medicine. 172 pages. The Macmillan Co., New York, 1937.

**OBSTETRICAL GUIDE.** By Philips J. Carter, M.D. From the Obstetrical Department of Louisiana State University Medical Center, New Orleans, La.

**LEHRBUCH DER FRAUENHEILKUNDE** (in zwei Baenden). Von Professor Dr. W. Weibel, Vorstand der II. Universitaets-Frauenklinik in Wien. Erster Band: Geburtshilfe. Mit 849 zum Teil mehrfarbigen Abbildungen im Text und 16 farbigen Tafeln, 647 Seiten. Urban und Schwarzenberg, Wien, 1937.



**CARCINOMA OF THE FEMALE GENITAL ORGANS.** By M. C. Malinowsky and E. Quater. Translated from the Russian by A. S. Schwartzmann, M.D. Illustrated, 255 pages. Published by Bruce Humphries, Inc., 306 Stuart Street, Boston, Mass.

**CHILDLESS.** A Study of Sterility, Its Causes and Treatment. By Sam Gordon Berkow, M.D. Illustrated, 307 pages. Published by Lee Furman, Inc., 381 Fourth Ave., New York City, 1937.

**KIDNEY PAIN,** Its Causation and Treatment. By J. Leon Jona, M.D., F.R.A.C.S., Hon. Asst. Gynaecological Surgeon, Women's Hospital in Melbourne. Illustrated, 94 pages. J. & A. Churchill, Ltd., London, 1937.

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## Items

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### **American Board of Obstetrics and Gynecology**

Practical oral and clinical examinations for Group A and B applicants will be held at Atlantic City, N. J., on June 7 and 8, 1937.

Applications for the Group A examination will be received in the office of the Secretary, Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh (6), Pa., to April 9, 1937. Application blanks may be secured from the Secretary's office.

### **Washington Gynecological Society**

The following officers were elected at the meeting held May 26, 1936: *President*, Dr. Prentiss Willson; *First Vice-President*, Dr. Jerome F. Crowley; *Second Vice-President*, Dr. Henry L. Darner; *Treasurer*, Dr. Radford Brown; *Historian*, Dr. John W. Warner; *Secretary*, Dr. Herbert P. Ramsey; *Council Member*, Dr. William J. Stanton (term expires 1940) and continuing on the *Council* are Drs. J. J. Mundell, J. Kotz, A. E. Pagan, and the retiring president, Dr. E. W. Titus.